ASSESSING CICLOSPORIN IN THE TREATMENT OF LEPROSY REACTIONS: EVIDENCE FROM A RANDOMIZED CONTROLLED TRIAL AND OTHER STUDIES

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DECLARATION BY CANDIDATE

I, Saba Maria Lambert, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

All the patients whose photographs are in this document have given signed permission to use their image.

Signed:  Date: 10/06/2014

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ABSTRACT

Leprosy patients present with a spectrum of skin lesions and neuropathy. Despite multi-drug therapy (MDT), which cures the infection, immunological reactions continue to occur, leading to disability and deformity secondary to neuropathy. Reactions are a major cause of morbidity and long term disability. The treatment of reactions is currently inadequate, with prednisolone being the main drug used with partial success and a high rate of side effects. Identifying better agents for treating leprosy reactions is an important clinical need with major service implications.

This work investigated the safety and efficacy of ciclosporin to treat reactions in leprosy patients in Ethiopia. A double-blind randomized controlled clinical trial comparing the efficacy and adverse event profiles of ciclosporin and prednisolone was conducted in patients presenting with Type 1 Reaction. Two similar pilot studies were conducted in patients with Erythema Nodosum Leprosum.

Validating the Type 1 Reaction Severity Scale in Ethiopian patients, assessing features of ENL severity and validating a quality of life questionnaire in Amharic were important preliminary projects to produce valid tools for measuring treatment outcomes.

Patients on ciclosporin and prednisolone had similar clinical outcomes in the treatment of new and chronic Type 1 Reaction. There was a high rate of Type 1 Reaction recurrence in both groups but the patients on ciclosporin required greater amounts of additional prednisolone to control these recurrences. Patients with acute ENL on ciclosporin had a significant 16-week delay in the onset of ENL recurrence. This important difference was not observed in patients with chronic ENL. Prednisolone related adverse events were much more frequent than those related to ciclosporin in all four studies.

For all my patients at ALERT who shared their world with me and taught me that however heavy the burden, there is always hope.

ACKNOWLEDGMENTS

The mention of Ethiopia, the land of my childhood, during the lecture on leprosy at the Liverpool School of Tropical Medicine given by Professor Diana Lockwood was enough to rekindle the thousand questions of my youth about leprosy. Professor Lockwood has been the most supportive supervisor and mentor I could have ever wished for during these last five years. Her perseverance, insight and encouragement have supported me throughout all the difficulties of setting up and running a clinical trial in Ethiopia as well as writing up this thesis.

I would like to thank the staff at ALERT Hospital and AHRI in Ethiopia: Dr Abraham Assefa, Dr Elsa Bizuneh and Dr Wim Brandsma who gave me all the initial advice and guidance to set up the project; Dr Ahmed Bedru and Dr Jemal Hussein who have given invaluable advice and guidance throughout; Dr Digafe Tsegaye and Dr Shimelis Nigusse Doni who were efficient study physicians and supportive friends; Asegid Alem Tura who was the most amazing study pharmacist; Abebe, Captain and Solomon who were the nurses; the runners Hanna and Yilma who kept everything running smoothly; the physiotherapists Tamiru, Demissew and Bayissa; the laboratory staff; the administration at ALERT, especially Ato Mezemir Ketema; the data management team run by Dr Lawrence Yamuah; Dr Munir, the pathologist; the members of Data Safety Monitoring Board: Dr Fuad Temam, Dr Getnet Yimer and Dr Girmay Medhin who gave me immensely valuable advice and guidance; and finally all the people I have forgotten to mention here.

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I would not have been able to complete this work without generous financial support from my funders, the Hospitals and Homes of St. Giles, London, UK and the German Leprosy Relief Association. Tony Griffiths and Geoff Holmes of Stiefel Laboratories Ltd. kindly donated the punch biopsy sets.

My family deserve more than my thanks: my husband Gaby who has had to learn all about leprosy and stand all the frustrations I brought home; my little boy Leo who was born in this period and has generously shared his mum with this work; my very special sister Rita, my brother Massimo and their lovely families who have continuously encouraged me; and my father and my Ethiopian family, including my parents-in-law, who have made my return to Ethiopia a special time. Special friends are precious: Anna and Theresa very kindly read through draft copies spotting all the errors that my eyes could no longer see; Rea patiently listened to numerous hours of moaning and with Matt prepared the randomization envelopes; and of course, all the friends who made me believe that one day I would successfully complete this project.

And finally, I thank my mother Francesca, whose fiery character and unwavering belief that I can achieve anything will keep me going into many more adventures…

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ABBREVIATIONS

AAERC	ALERT and AHRI Ethics Review Committee
AE	Adverse event
AFB	Acid-fast bacilli
AHRI	Armauer Hansen Research Institute
ALERT	All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre
AMFES	ALERT MDT Field Evaluation Study
APC	Antigen-presenting cell
APC	Antigen presenting cell
AR	Adverse reaction
BANDS	Bangladesh Acute Nerve Damage Study
BB	Borderline borderline
BCG	Bacille Calmette-Guerin
BI	Bacterial index
BL	Borderline lepromatous
BP	Bodily pain scale
BT	Borderline tuberculoid
CD	Cluster of differentiation
CMI	Cell mediated immunity
Cn	Ciclosporin
DACA	Drug Authorization and Administration Authority
DLL	Diffuse lepromatous leprosy
DNA	Deoxyribonucleic acid
DSMB	Data Safety and Monitoring Board
EHF	Eye Hand Foot score
ENL	Erythema Nodosum Leprosum
FMOH	Federal Ministry of Health
FROM	Full range of movement
g, mg, ng, kg	Gram, milligram, nanogram, kilogram
GCP	Good Clinical Practice
GH	General Health scale

GILZ	Glucocorticoid-induced leucine zipper
GMP	Good Manufacturing Practice
GR	Glucorticoid receptor
GRE	Glucocorticoid response elements
HAART	Highly Active Antiretroviral Therapy
HAT	Histone acetyl transferases
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigens
HRQOL	Health Related Quality of Life
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFNγ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
ILEP	International Federation of Anti-Leprosy Associations
IMP	Investigational medicinal product
INFIR	ILEP Nerve Function Impairment and Reaction
iNOS	Inducible nitric oxide
IQR	Inter-quartile range
IRIS	Immune reconstitution inflammatory syndrome
IV	Intravenous
IκBα	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
LL	Lepromatous leprosy
LSHTM	London School of Hygiene and Tropical Medicine
MAP	Mitogen-activated protein
MB	Multibacillary
MCS	Mental health component summary score
MDT	Multi-drug therapy
MF	Monofilament
MH	Mental Health scale
MHC	Major histocompatibility complex
Mtb	M. tuberculosis

NERC	National Ethics Review Committee (Ethiopia)
NFAT	Nuclear factor of activated cell
NFI	Nerve function impairment
OR	Odds Ratio
P or Pred	Prednisolone
PB	Paucibacillary
PCR	Polymerase chain reaction
PCS	Physical health component summary score
PF	Physical functioning scale
PGL	Phenolic glycolipids
PI	Principal investigator
PNL	Pure neuritic leprosy
PO	per os (orally)
POD	Prevention of Disability
QOL	Quality of Life
RCT	Randomized controlled trials
RE	Emotional Role scale
R-J	Ridley -Jopling
RP	Physical Role scale
RR	Reversal Reaction
Rx	Treatment
SAE/SAR	Serious Adverse Event/ Reaction
SD	Standard deviation
SF	Social functioning scale
SN	Silent neuropathy
SPSS	Statistical Package for the Social Sciences
SSAR	Suspected Serious Adverse Reaction
ST	Sensory testing
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWM	Semmes-Weinstein monofilaments
T1R	Type 1 Reaction
TB	Tuberculosis
TENLEP	Treatment of Early Neuropathy in LEProsy

Th	T helper
TNF	Tumour necrosis factor
TRIPOD	Trials In Prevention of Disability
TT	Tuberculoid (leprosy)
VMT	Voluntary muscle testing
VT	Vitality scale
WHO	World Health Organization

CHAPTER 1 INTRODUCTION

The Problem

Research hypothesis

Aims and Objectives

Structure of the thesis

Ethiopia: study setting

A historical overview of leprosy in Ethiopia

Ethiopia's health care system

Leprosy situation in Ethiopia

Study site: ALERT and the Red Medical Clinic

1.1 THE PROBLEM

Leprosy, or Hansen's disease, is one of the oldest diseases afflicting mankind. Multi-drug therapy (MDT) cures the infection by *Mycobacterium leprae*. Although the bacteria may be eliminated, the damage done to nerves by the bacteria and by consequent immunological reactions leads to very visible and stigmatizing disabilities and deformities.

The management of these leprosy related immunological reactions remains challenging. Oral prednisolone, the drug of choice, has frequent side effects and approximately 40% of individuals do not show clinical improvement. There is a lack of efficacious and safe second line treatments for both Type 1 Reaction (T1R) and Erythema Nodosum Leprosum (ENL).

This research investigates the efficacy and safety of ciclosporin as an alternative to the standard prednisolone treatment in immunological reactions. Potentially useful tools in leprosy clinical trials such as a quality of life assessment and severity scales for leprosy reactions are also assessed.

1.2 RESEARCH HYPOTHESIS

We hypothesise from laboratory studies and previous clinical studies that the effects of ciclosporin on the T cell immune response make it a potentially useful agent in the treatment of leprosy T1Rs, acute neuritis and ENL. Our hypothesis is, that in the management of leprosy reactions:

1. Ciclosporin is as effective as prednisolone in the treatment of patients with leprosy reactions and nerve function impairment.

2. Patients treated with ciclosporin have fewer side effects than patients treated with prednisolone.

1.3 AIMS AND OBJECTIVES

Our aims and objectives were to:

1. Test the Hypothesis of Non-Inferiority for ciclosporin versus prednisolone (i.e. ciclosporin is as effective as prednisolone) in the management of leprosy reactions
2. Record the side-effect profiles of ciclosporin and prednisolone in the management of leprosy reactions
3. Validate the Clinical Severity Scale for Type 1 Reaction in Ethiopian patients and use it in the clinical trial to assess improvement
4. Identify a possible clinical severity scoring system for ENL
5. Translate and validate a quality of life questionnaire in Amharic and use it to measure the patient's assessment of the treatment effect

1.4 STRUCTURE OF THE THESIS

This thesis addresses the lack of effective treatments for leprosy patients with either Type 1 Reaction or Erythema Nodosum Leprosum. Four clinical trials were done assessing the effectiveness of ciclosporin in the management of leprosy reactions. The trials and their specific aims and objectives are listed below:

Study 1A: Ciclosporin in the management of new Type 1 Reactions in leprosy

Aim: To determine whether patients with new Type 1 Reactions treated with ciclosporin have the same treatment outcome as those treated with prednisolone.

Objective: A randomised controlled trial comparing ciclosporin and prednisolone in the treatment of new leprosy Type 1 Reactions.

Study 1B: Ciclosporin in the management of chronic or recurrent Type 1 Reactions

Aim: To determine whether ciclosporin can be used to treat patients with chronic or recurrent Type 1 Reactions, which are not controlled by standard prednisolone regimens.

Objective: A pilot study assessing the efficacy and safety of ciclosporin as a second-line drug in patients with Type 1 Reactions who have not responded to a 12-week course of prednisolone.

Study 2A: Ciclosporin in the management of new Erythema Nodosum Leprosum

Aim: To assess the safety, tolerability and efficacy of ciclosporin in the treatment of patients with new acute ENL.

Objective: A double-blind controlled pilot study randomizing patients with new acute ENL to treatment with either ciclosporin or prednisolone.

Study 2B: Ciclosporin in the management of chronic or recurrent ENL

Aim: To assess the safety, tolerability and efficacy of ciclosporin in the treatment of patients whose ENL is not controlled with standard prednisolone regimens.

Objective: A double-blind controlled pilot study randomizing patients whose ENL is not controlled with standard prednisolone, and comparing a group treated with ciclosporin to a group treated with additional steroid only.

The trials were all carried out at ALERT hospital in Addis Ababa, Ethiopia.

Chapter 1 outlines the reason for carrying out this research and describes the setting of the study. Chapter 2, the literature review, gives a general introduction on leprosy, its complications and management thus providing a framework for this study. In Chapter 3, tools to measure severity of reactions are assessed. Chapter 4 describes the translation and validation of a tool to measure quality of life in Amharic in order to use it as an outcome measure in leprosy clinical trials. In Chapter 5, the trial design and methods are described, as well as on-site adjustments made in order to run the study efficiently. In Chapter 6 and 7, the results of the study of ciclosporin in T1R and ENL are provided respectively. Finally, based on the conclusions from this research, some recommendations for future research areas are made in Chapter 8.

My roles in this study included writing the grant proposal, and designing the studies. I was responsible for obtaining the various ethical approvals, for the design and writing of trial forms, consent forms and patient information sheets. I initiated contact with various pharmaceutical companies in order to obtain prednisolone,

ciclosporin and placebo drugs. I worked as a full time physician in the leprosy clinic during the study period. Two other Ethiopian dermatologists were also involved as study physicians to monitor and review patients on the study. I performed the first set of data entry, whilst the second entry was done by data managers at ALERT. Data analysis was performed by me with guidance from Peter Nicholls, the study statistician.

1.5 ETHIOPIA: STUDY SETTING

1.1.1 A historical overview of leprosy in Ethiopia

Genomic studies point to East Africa as the likely origin of *M.Leprae* (Monot *et al.*, 2005), making Ethiopia not only the land of the oldest hominid, but possibly the "cradle of leprosy".

Leprosy is mentioned in ancient Ethiopian documents and religious texts as well as in the Ethiopian folklore (Figure 1.1). The first European to record leprosy in Ethiopia was Portuguese missionary Alvares, in 1520. In the Orthodox Christian-dominated areas, the socio-religious and political values of alms giving were so deeply-rooted, leading to a compassionate social attitude towards "leprosy-sufferers". These leprosy-affected people practiced the Hamina song-mendicant tradition which was partially the result of popular belief that leprosy was hereditary and that the symptoms of the disease could be relieved by singing while begging (Kebede, 2010).

At the turn of the twentieth century, information that leprosy was a contagious disease was arriving in Ethiopia and with it, the idea that isolation of people affected by leprosy was the way to avert spread of the disease. In 1901, the first Ethiopian leprosarium was founded by French Catholic missionaries in Harar. With the Italian invasion of Ethiopia in 1935, forced segregation of leprosy-affected people and their families was introduced, resulting in the sudden growth of the leprosaria. The number of patients at the Princess Zenebwork Leprosarium in Addis Ababa grew from less than 100 to more than 1000 in a few years. With the hope of a cure offered by the introduction of dapsone injections in the 1950s, more leprosy-affected people

flocked to the leprosaria, with numbers at the Princess Zenebwork Leprosarium reaching 3000. This population pressure lead to the establishment of other leprosaria in the 1950's and 1960's (Kebede, 2005).

In total ten leprosaria were opened throughout Ethiopia. With the advent of MDT, patient rehabilitation and decentralization of leprosy treatment, only five leprosy centres (general hospitals with a leprosy unit) remain. Princess Zenebwork Leprosarium in Addis Ababa is now called ALERT (All Africa Leprosy, Tuberculosis Rehabilitation Training) Centre and is the tertiary referral centre for leprosy management.

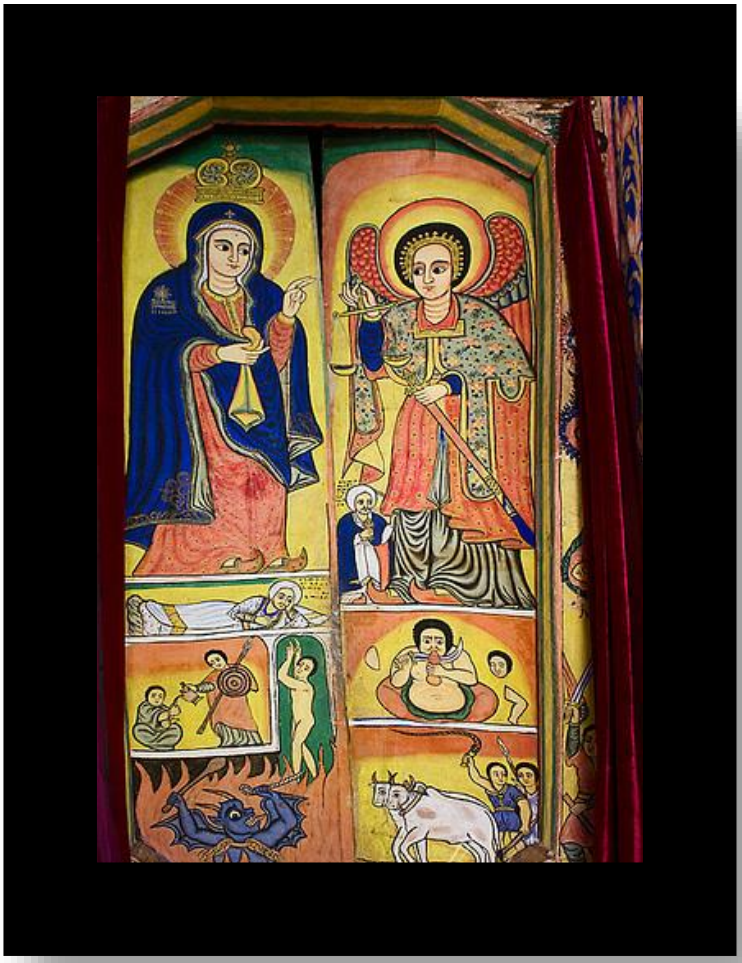


Figure 1.1 Ancient church painting

The life of Semeon, the Cannibal, is depicted as it appears in the book of Miracles of St Mary. He devoured seventy-eight people including his wife, children and relatives. At the end of the day, however, Simon managed to inherit the Kingdom of Heaven for his alms of half-a-drink of water to a leper beggar, who was begging in the name of St. Mary.

1.1.2 Ethiopia's health care system

Ethiopia may be among the least developed countries in the world but it is rapidly modernizing. The latest population estimate stands at 84.32 million (Central Statistical Agency, 2012), with an average life expectancy of 62 years. It has an estimated per capita income of US$ 412 (World Bank 2012).

Ethiopia has a federal system where power is decentralized to nine Regional States and the City Administration Councils of two cities: Dire Dawa and Addis Ababa (Figure 1.2), which are sub divided into 817 administrative Woredas (districts). Ethiopia has adopted a three-tier health system with special emphasis on primary health care delivery. The first level is a Woreda (District) health system comprising of a primary hospital for about 100 000 people, at least five health centres per 25 000 population and 25 satellite health posts (HPs) per 3 000-5 000 population. The second level is a General Hospital for one million people, and the third is a Specialized Hospital for a population of five million. At present it is estimated that Ethiopia has one doctor per 40 000 people compared to a regional average of 2.2 doctors per 10 000 people.

1.1.3 Leprosy situation in Ethiopia

The Ministry of Health in Ethiopia generates annual statistics based on reports from the Regional Health Bureaus, which are forwarded to the WHO every year. Every Health Centre in Ethiopia is supposed to maintain a leprosy case registration book recording treatment dispensation and disability status. Distribution of leprosy cases remains localized to the highland areas, with about 90% of cases in three main regions (Oromia, Amhara and SNNP), with a few well known pocket areas (Figure 1.2).

Leprosy services have been integrated into the general health services at all levels since 2001. General Health Workers at Health Centres are theoretically supposed to be able to diagnose leprosy as well as supply MDT, only referring patients with complications such as reactions to one of the five leprosy referral centres. In practice, health staff training on leprosy is poor and rapid staff turn-over is a major problem,

resulting in loss of skills. Patients are thus at risk of delayed diagnosis, which is worsened by delayed presentation of the patient, which in turn is influenced by traditional beliefs about leprosy, and poverty (inability to afford transport costs). Delayed presentation and delayed diagnosis are major influencing factors in grade-2 disability rates.

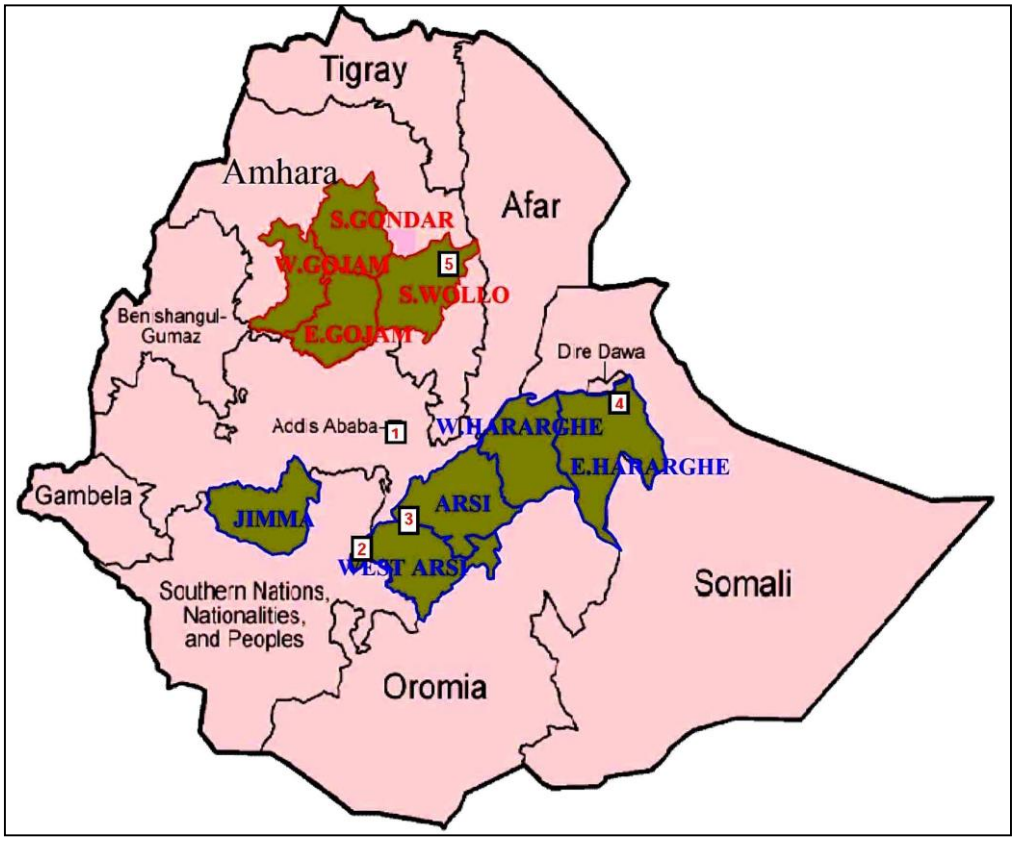


Figure 1.2 Map of Ethiopia

Showing the nine regions and two administrative cities; in green are the areas with high cases of leprosy. Leprosy referral centres are: 1. ALERT; 2.Kuyera; 3. Gambo; 4. Bisidimo and 5.Boromeda.

In 2012, 3776 new cases of leprosy were registered, putting Ethiopia in second place after Nigeria (3805), on the African continent, and in fifth place globally (WHO, 2013). New leprosy case numbers in Ethiopia have been stable for many years. Figure 1.3 shows the very gradual decrease in new leprosy cases reported, but there are concerns about under-diagnosis and inaccurate recording. There are no population screening programmes or contact tracing programmes. The majority of new patients self-present at Health Centres or Referral Centres; many cases presenting late with advanced lepromatous leprosy and advanced disability. Child

leprosy rate stands at around 7-9% nationally. These statistics point to on-going leprosy transmission in Ethiopia.

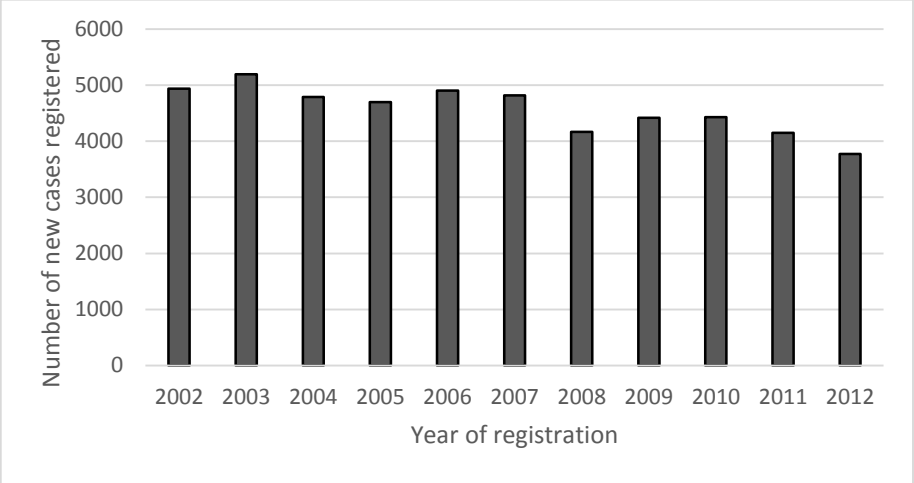


Figure 1.3 Number of new cases of leprosy registered in Ethiopia, in the last 10 years as per FMOH statistics (WHO, 2013)**.**

Table 1.1 shows a decreasing rate of disability grade-2 in patients with newly diagnosed leprosy in the last 10 years. Local experience shows that disability grading is often not assessed (or not reported), or done inaccurately. A recent knowledge, attitude and practice (KAP) survey was conducted in eight zones, interviewing 601 general health workers in leprosy endemic areas of Ethiopia. Ninety percent of the health workers interviewed were unable to correctly grade the disability status in leprosy patients (Abeje *et al.*, 2013).

Year	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Percentage of new patients with gr-2 disability	**14.8**	**14.9**	**14.5**	**12.5**	**10.7**	**10**	**9**	**7**	**9**	**7**	**6.9**

Table 1.1 Percentage of new leprosy cases with grade-2 disability as per FMOH statistics for Ethiopia (WHO, 2013)**.**

A report published by Gambo, a leprosy referral centre in Ethiopia, showed grade-2 disability rate amongst 210 newly diagnosed leprosy patients (1999-2009) at 35.6% (Ramos *et al.*, 2011). These data are similar to more recent reports at ALERT

hospital where grade-2 disability in newly diagnosed patients varies between 8% and 27%. Although referral centre data are thought to be biased towards having more disabled patients being seen there, the fact that the majority of new patient self-refer at both centres raises questions about the accuracy of the national data.

Despite training, guidelines and manuals on field management of reactions, reaction recognition and management remains poor. The KAP survey mentioned above found that only 17% of the staff interviewed were able to correctly list the signs and symptoms of leprosy reaction, and the overwhelming majority (97%), did not know how to manage reactions. Prednisolone is manufactured in Ethiopia, and is usually available at referral centres and private pharmacies, but many health centres do not stock it. Patients still have to travel long distances, at great cost, to obtain reaction treatment. The monitoring of treatment for patients in reaction is also poor as standard regimens of prednisolone tend to be followed by protocol rather than varying treatment according to patient response.

1.1.4 Study site: ALERT and the Red Medical Clinic

ALERT hospital is situated in what used to be the outskirts but is now a relatively poor suburb of Addis Ababa. Many of the patients using the services at ALERT live in the surrounding slums and are either ex-leprosy patients or descendants of leprosy patients. New patients with suspected leprosy often prefer to travel long distances to be treated at ALERT because of the good reputation of the hospital. Many refuse to go back to their own rural homes because of the fear of stigma they and their relatives might suffer from. They tend to settle in the slums around ALERT hospital where they can easily access free medical care, live with people who understand their condition and earn a living with manual jobs in the city.

ALERT Centre is the national referral centre for leprosy related complications and it is a large facility containing all the leprosy related specialties: Dermatology, Ophthalmology, Orthopaedics, Orthotics, Plastic Surgery, Physiotherapy, Occupational Therapy and a Rehabilitation Program. A functioning laboratory and pharmacy are also on-site. ALERT Centre was originally funded and run by foreign non-governmental organizations but was handed over to the Ministry of Health of Ethiopia in 2004. It is currently a 240-bed teaching general hospital with a multi-

drug resistant tuberculosis unit and a large HIV unit added in since the take-over by the Ministry of Health. ALERT Centre also has a training centre for leprosy and is associated with the Armauer Hansen Research Institute (AHRI), established in 1970, specializing in research related to TB, leprosy, leishmania, meningitis, HIV and cholera.

Leprosy services at ALERT are covered by the Red Medical Clinic which is staffed by a dermatologist and two specialist nurses. Patients are seen here for leprosy diagnosis and leprosy reaction treatment. MDT is dispensed at the local clinic just outside ALERT if the patient resides in the neighbourhood, or if from further afield, at their local Health Centre. It is not uncommon for Health Centres to run out of MDT supplies and for patients to travel back to ALERT in search of MDT.

When I started at ALERT in 2009, I encountered many difficulties as the Red Medical Clinic services were running on survival mode. With a changeover in management and new management style, staff turn-over was high. There were medication shortages as the pharmacy changes resulted in delays in ordering new supplies; laboratory services were scaled back and staff morale was low. Feeling it was impossible to run any kind of clinical trial under such circumstances, I took over as main physician at the Red Medical Clinic with the aim of reviving leprosy services and stabilizing the situation in the clinic until other staff could take over. As well as preparing the grounds for this clinical trial, I spent my first year at ALERT working as a full time physician in the field of leprosy gaining invaluable experience. Full record-keeping was re-instituted, patient care pathways and guidelines updated, patient flow was improved and regular patient education/self-care sessions became routine. Being registered as a medical practitioner in Ethiopia and being able to fluently speak two of the main Ethiopian languages, Amharic and Tigrigna, were major facilitating factors enabling me to work effectively in the clinic.

A typical monthly activity report is shown for the month of February 2013 (Figure 1.5). An average of 27 new leprosy patients are diagnosed in the Red Medical Clinic every month with around 250 patients a month attending for leprosy reactions or other complications such as ulcers.

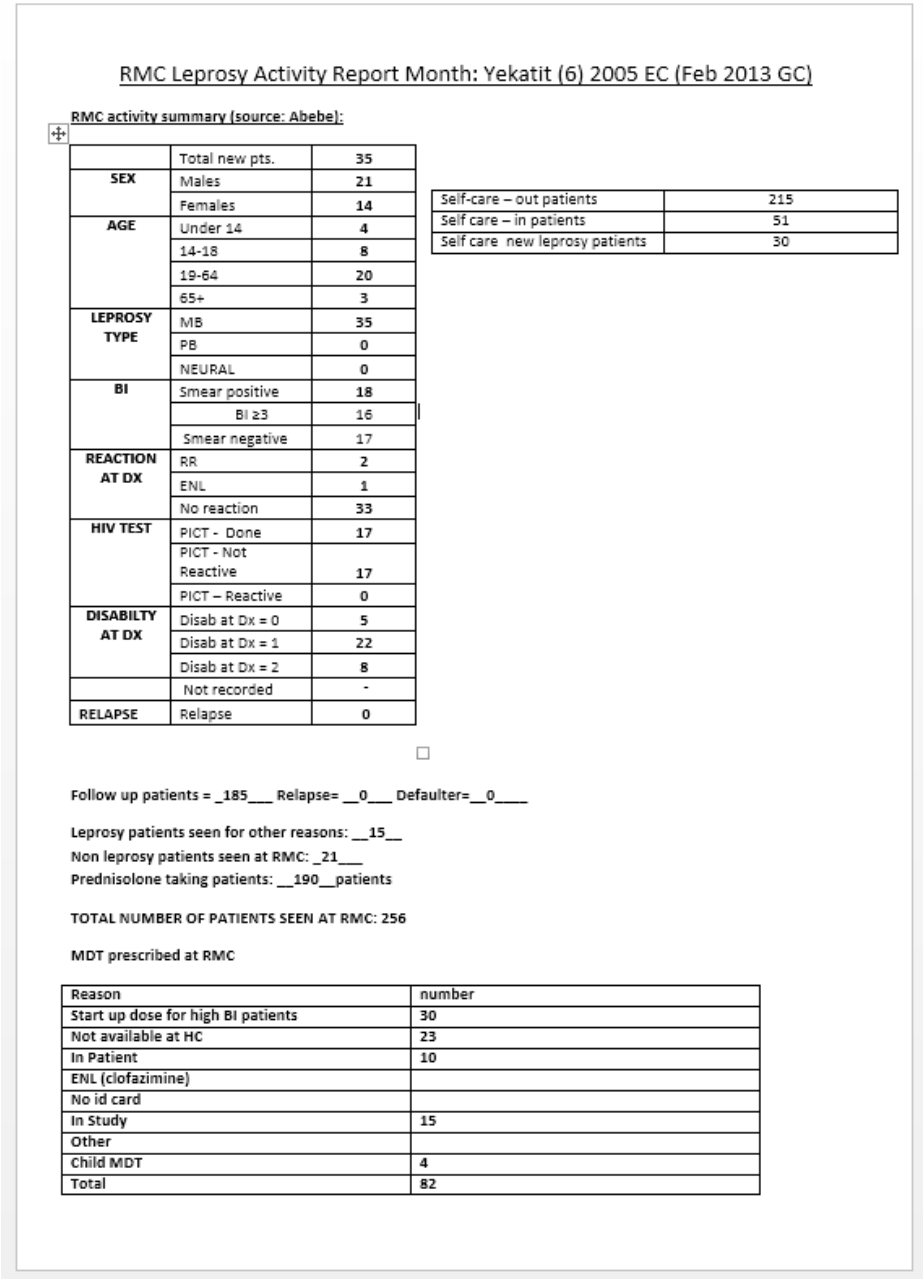
HIV testing with pre- and post-test counselling is now done for the majority of newly diagnosed leprosy patients as well as for patients presenting with recurrent reactions or any symptoms of immune-suppression. We also obtained special permission from

the Ministry of Health to be able to dispense MDT from the ALERT pharmacy and a record of reasons for prescribing MDT is kept for future service planning.

Figure 1.4 Working in the Red Medical Clinic

In 2011, 316 new leprosy patients were diagnosed at ALERT: 68% of these were male, 6% were children under 14 and 5% were aged over 65. Most patients (98%) were diagnosed with MB leprosy, with 46% having a positive BI on slit-skin smear, of which 36% had a BI of 3 and above. Many patients tend to seek medical help once they are experiencing a painful and debilitating leprosy reaction. In 2011, 21% of patients had Type 1 Reaction and 15% had ENL at the time of their leprosy diagnosis. Of the 131 patients screened for HIV, four tested positive. In terms of disability grading at diagnosis, 27% of patients already had visible grade-2 disability, and 45 % grade-1 disability. Reasons for late presentation given by patients included fear of stigma, time spent seeking alternative traditional treatment or retreating for Holy Water therapy at special monasteries, and misdiagnosis at Health Centres or by private doctors.

The statistics above show that ALERT hospital has a busy leprosy clinic that with some organizational input was an ideal site for our clinical trials. Enough patients with leprosy reactions were presenting at ALERT, hospital beds were available for severe cases and patients living within 100km radius could be recruited as out-patients. The transport costs and other medical costs would be covered by the study.



RMC Leprosy Activity Report Month: Yekatit (6) 2005 EC (Feb 2013 GC)

RMC activity summary (source: Abebe):

	Total new pts.	35
SEX	Males	21
	Females	14
AGE	Under 14	4
	14-18	8
	19-64	20
	65+	3
LEPROSY TYPE	MB	35
	PB	0
	NEURAL	0
BI	Smear positive	18
	BI ≥3	16
	Smear negative	17
REACTION AT DX	RR	2
	ENL	1
	No reaction	33
HIV TEST	PICT - Done	17
	PICT - Not Reactive	17
	PICT – Reactive	0
DISABILTY AT DX	Disab at Dx = 0	5
	Disab at Dx = 1	22
	Disab at Dx = 2	8
	Not recorded	-
RELAPSE	Relapse	0

Self-care – out patients	215
Self care – in patients	51
Self care new leprosy patients	30

Follow up patients = _185___ Relapse= __0___ Defaulter=__0____

Leprosy patients seen for other reasons: __15__
Non leprosy patients seen at RMC: _21___
Prednisolone taking patients: __190__patients

TOTAL NUMBER OF PATIENTS SEEN AT RMC: 256

MDT prescribed at RMC

Reason	number
Start up dose for high BI patients	30
Not available at HC	23
In Patient	10
ENL (clofazimine)	
No id card	
In Study	15
Other	
Child MDT	4
Total	82

Figure 1.5 Monthly activity report for Red Medical Clinic , (EC=Ethiopian calendar)

Whilst waiting to obtain the various approvals needed for the clinical trials, I started our other LSHTM-ALERT collaborative study: a long-term observational study looking at patients co-infected with leprosy and HIV. This study served as practice run for patient flow and study operational guidelines for the clinical trial. It was also during this period that we evaluated and validated the Amharic Health Related Quality of Life questionnaire and the Clinical Severity Scale for T1R, and looked at a possible severity grading system for ENL.

CHAPTER 2 LITERATURE REVIEW

Literature Review of Leprosy

Epidemiology
The causative organism
Transmission and genetic susceptibility
Pathology
Immunology of leprosy
Clinical features
Differential diagnosis
Diagnosis and Investigations
Classification of leprosy
Nerve function assessment
Disability grading
Treatment of *M.leprae* infection
Management of leprosy and prevention of disability
Leprosy and pregnancy
Leprosy and HIV

Literature Review of Leprosy Reactions

Type 1 reactions: Epidemiology; Risk factors; Genetic regulation; Pathology; Immunology; Clinical features;
Measuring severity of T1R

ENL: Epidemiology; Risk factors; Genetic regulation; Pathology; Immunology; Clinical features;
Measuring severity of ENL

Literature Review of Reactions Treatment

Prednisolone
Prednisolone adverse effects
Prednisolone in Leprosy Reactions
Mode of action
Effectiveness of prednisolone in T1R
Alternatives to prednisolone in T1R
Effectiveness of prednisolone in ENL
Alternatives to Prednisolone in ENL
Adverse Effects of prednisolone in Reactions

Ciclosporin
Ciclosporin adverse effects
Ciclosporin in Leprosy Reactions
Ciclosporin in T1R
Ciclosporin in ENL

Note on the literature review:

This literature review was performed using keywords "leprosy", "Hansen's disease", "Type 1 Reaction", "Reversal Reaction", erythema nodosum leprosum", " ENL", "prednisolone" , "ciclosporin" in Embase and PubMed engines to search through Ovid and Medline publication databases respectively. WHO documents on leprosy were also checked on the WHO website. Additional references were gathered from conference programs, article citations, and Google internet searches, as well previous PhD thesis available on EThOS and at the LSHTM library.

2.1 LITERATURE REVIEW OF LEPROSY

Leprosy is a chronic granulomatous infection, principally affecting the skin and peripheral nerves, caused by the obligate intracellular organism, *Mycobacterium leprae* (Lockwood, 2004).

2.1.1 Epidemiology

The existence of people affected by leprosy in China, India and Egypt in about 600 B.C. has been described in ancient texts (Robbins *et al.*, 2009). Today, almost every country in the world reports at least one case of leprosy. Some highly endemic leprosy pockets, mainly in tropical regions of the world, continue to persist. In 2012, 232 857 new cases were registered worldwide and reported to the World Health Organization (WHO, 2013). At the beginning of 2013, the global registered prevalence of leprosy cases was 189 018.

The decline in leprosy prevalence from 1.2 million cases in 1995 to 189 018 in 2013 is partly due to a change in the definition of prevalence and a decrease in the length of duration of treatment. The registered prevalence of leprosy is defined as the number of patients registered for treatment on December 31st of a given year. An accurate estimate of the actual prevalence of the disease is not possible because of the long incubation periods. The rate of decline in the number of new cases of leprosy detected during 2006-2012 was modest compared to earlier years. The

number of cases reported to the WHO is dependent on operational factors such as correct diagnosis and registration in the field as well as the political will of different countries to report accurately and on time (Fine, 2008). A Brazilian study (Moura *et al.*, 2013) confirmed previous findings by an Indian study (Shetty *et al.*, 2009) that active case finding amongst household contacts or the general public increases the incidence rate by two to nine fold. In the Indian study, 35% of new cases were children indicating that active transmission was occurring. Leprosy transmission has not been interrupted in many countries, despite 25 years of MDT.

The 2013 WHO report also shows that in many regions the number of new cases reported annually is increasing. The top eight endemic countries are India, Brazil, Indonesia, Nigeria, Ethiopia, Bangladesh, Democratic Republic of Congo, and Nepal. Most cases occur in the developing world (Figure 2.1).

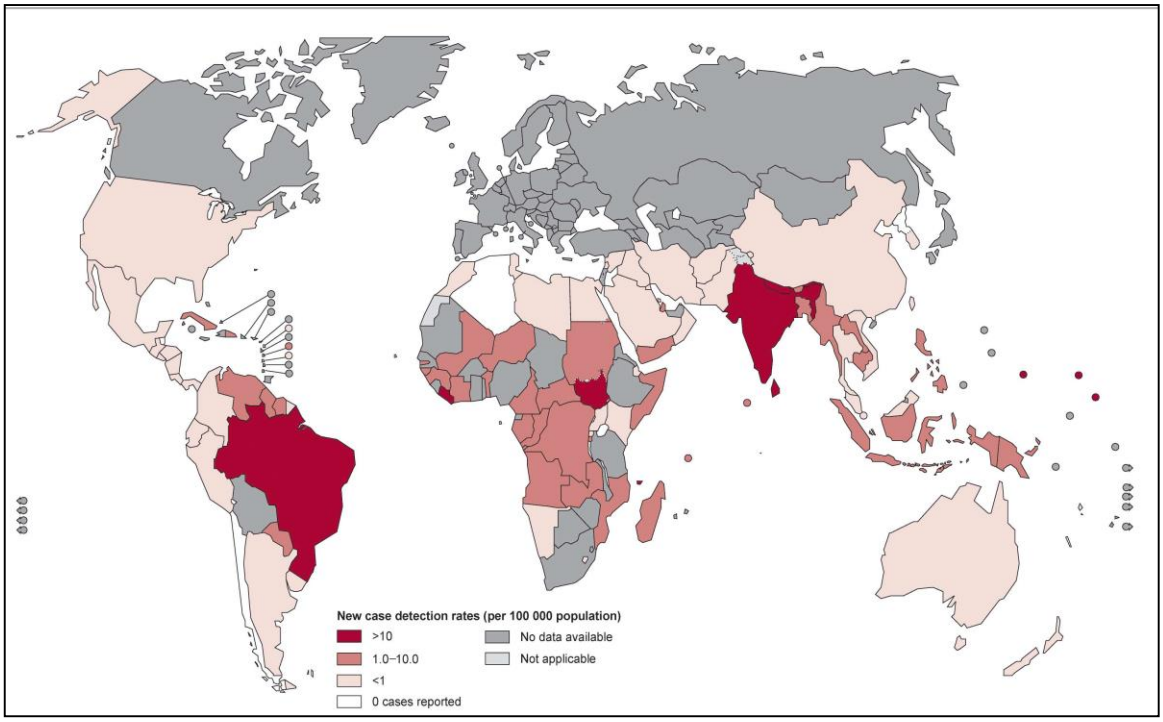


Figure 2.1 WHO Map of leprosy new case detection rates, January 2012

The profile of newly detected cases shows that in Africa up to 89.52% of cases are multibacillary. The variation in the percentage of female from 20% to 57% between countries may reflects in part a social rather than biological factor. The percentage of children amongst new cases, varies between 1% and 38%. Recording disability rates amongst newly diagnosed cases is now becoming an important marker in leprosy

control. One of the objectives of the Enhanced Global Strategy for Further Reducing the Disease Burden due to Leprosy 2011-2015, is to reduce the global rate of new cases with grade-2 (i.e. visible) disabilities per 100 000 population by at least 35% by the end of 2015, compared with the baseline at the end of 2010 (WHO, 2009a). This approach underlines the importance of early detection and quality of care in an integrated service setting. In 2012, the global rate of new cases with grade-2 disabilities per 100 000 was 0.25, with the rate for Africa being 0.40 (WHO, 2013).

2.1.2 The causative organism

Leprosy is caused by *Mycobacterium leprae*, a rod-shaped, gram positive organism that is acid-fast when stained by the Ziehl-Nielsen method. It is an obligate intracellular organism. It was first identified in the nodules of lepromatous leprosy patients by G.H. Armauer Hansen in 1873, making it the first bacterium to be identified as causing human disease (Hansen, 1874). *M.leprae* binds to skin macrophages and peripheral nerve Schwann cells. A major obstacle to progress in leprosy research has been the inability to culture *M.leprae* in vitro. It can be obtained following prolonged growth in the mouse footpad (Shepard, 1960) and the nine-banded armadillo. *M.leprae* collected from human nasal mucus and injected in the footpad of the mouse *M.leprae,* has a very slow doubling time of approximately two weeks (Levy & Ji, 2006). Optimum temperature for growth is 30-33°C. Lesions caused by *M.leprae* are known to commonly occur in cooler parts of the body such as nose, ears, buttocks and extremities. Desikan has reported on the survival of *M.leprae* from nasal secretions up to nine days outside the human body, under tropical conditions (Desikan & Sreevatsa, 1995). Man and the armadillo are natural reservoirs of *M.leprae*. Leprosy may be considered as a zoonosis in southern United States (Truman *et al.*, 2011), but the epidemiological significance of the armadillo is negligible.

In 2001 the genome of *M.leprae* was fully sequenced (Cole *et al.*, 2001). The organism appears to have undergone extensive reductive evolution with considerable downsizing of its genome compared with *Mycobacterium tuberculosis*. Almost half of the genome is occupied by pseudogenes. This gene loss leaves *M.leprae* unable to respond to different environments and its dependance on the host cell for essential

metabolic requirements probably explains the impossibility of growing the organism in vitro. Genome decay and the presence of such a large number of pseudogenes suggested that much genetic diversity should exist among *M.leprae* strains. However, comparative genomics revealed variation to be exceptionally rare (Singh & Cole, 2011). *Mycobacterium lepromatosis* first described in 2008, has been the only other identified pathogen associated with diffuse lepromatous leprosy, also known as Lucio's leprosy (Han *et al.*, 2009).

2.1.3 Transmission and genetic susceptibility

Transmission studies are difficult in leprosy because of the unique biology of the organism and the long incubation period of disease. Leprosy has an insidious onset, and the source of the infection in an infected individual is rarely identified. Individuals with active disease are thought to be the main source of infection (Job *et al.*, 2008). Two to four years is considered the usual incubation period in leprosy, although periods from three months to 40 years have been recorded (Bryceson & Pfaltzgraff, 1990).

The two main exit routes of *M.leprae* from the human body are the nasal mucosa and the skin. Patients with lepromatous leprosy harbour most bacilli in their skin, but bacilli are seldom shed from intact skin. Nasal mucosa of these patients is also heavily infected with *M.leprae*; the daily discharge of viable bacilli in nasal secretions can be as high as ten million (Davey & Rees, 1974). Studies detecting *M.leprae* DNA by polymerase chain reaction (PCR) in nasal secretions have shown that, in leprosy endemic countries, *M.leprae* DNA is carried by normal individuals and by contacts of cases. In Ethiopia, *M.leprae* DNA was detected by PCR on nasal swabs in approximately six per cent of 664 participants with no signs of leprosy (Beyene *et al.*, 2003). These asymptomatic individuals may be able to transmit the infection through nasal droplets.

The entry route of *M.leprae* into the human body is also not definitely known. The first clinical lesion is usually on the skin and occasionally a peripheral nerve is affected first. The most common route of entry is the nose, but leprosy has occasionally occurred following presumed inoculation through the skin during surgical procedures, tattooing or accidental trauma (Brandsma *et al.*, 2005).

It is hypothesised that following contact with an infective dose of *M.leprae*, most people will develop adequate protective immunity and therefore will not develop any clinically detectable signs or symptoms (Hatta *et al.*, 1995). The host response in these cases is thought to be entirely cell mediated with well-developed hypersensitivity. T helper cells driven by IL2 lead to macrophage activation and bacillary destruction, thus controlling any signs of disease. A study in Ethiopia, at a time when prevalence of leprosy was estimated at 1%, demonstrated that 50% of subjects with household or occupational contact with leprosy for at least a year had immunological evidence of exposure to *M.leprae*, suggesting that the great majority of people who become infected develop subclinical, immunizing infection (Godal & Negassi, 1973).

Genetic susceptibility is thought to be of importance not only in predisposing or protecting against developing clinical disease, but also in determining the clinical features of the disease in individuals. An Indian study demonstrated higher concordance rates for leprosy among monozygotic compared to dizygotic twins (Ali, 1966). Various genes and regions in the human genome have been linked to or associated with susceptibility to leprosy per se or with a particular type of leprosy. The human leucocyte antigens (HLA) encoded by both class I and class II genes of the major histocompatibility complex (MHC) have been studied in a wide variety of leprosy patients. A leprosy susceptibility locus (PARK2 and PACRG genes) has been mapped to chromosome 6q25–q26 in Vietnamese and Brazilian families with leprosy (Mira *et al.*, 2004). A genome-wide association study on 706 leprosy patients and 1225 controls showed that variants of genes in the NOD2-mediated signalling pathway (which regulates the innate immune response) are associated with susceptibility to infection with *M.leprae* (Zhang *et al.*, 2009).

Contacts of leprosy patients are at higher risk of developing the disease than the general population. The risk for household contacts of multibacillary patients in Malawi was up to eight times that of the general population and twice that of contacts of paucibacillary patients (Fine *et al.*, 1997). In a Brazilian study, in which 1352 high risk household contacts of 444 multibacillary patients were identified, 13.8% tested positive by ELISA anti-PGL-I serology showing that they had been exposed to *M.leprae* and had mounted an immune response. Another 4.7% had *M.leprae* DNA identified on PCR from nasal swabs (Araújo *et al.*, 2012); these

contacts may be at risk of leprosy infection as well as acting as a source for leprosy transmission.

Chemoprophylaxis of these contacts may improve bacillary clearance and interrupt leprosy transmission. Chemoprophylaxis in the form of a single dose of rifampicin is known to lower the incidence of leprosy in social contacts, although the effect is only seen in the first two years (Moet *et al.*, 2008). Considering the long incubation period of leprosy, the efficacy of rifampicin prophylaxis needs further research. Vaccination with BCG, given to prevent tuberculosis, seems to be the most efficient method of preventing leprosy (Smith & Saunderson, 2010). BCG vaccination of contacts seems to be protective even in contacts who have already had neonatal BCG (Schuring *et al.*, 2009; Düppre *et al.*, 2008). With the development of new TB vaccines, it is important to explore new vaccines for leprosy or adding protection against leprosy in any new vaccine (Rodrigues & Lockwood, 2011).

The current recommendation in WHO's Enhanced Global Strategy for Further Reducing the Disease Burden due to Leprosy (WHO, 2009a) is to examine household contacts of patients for evidence of leprosy, to educate the contacts on early signs of the disease, and to advise them to return for examination if any signs develop.

2.1.4 Pathology

The pathology of leprosy is determined by host immune response. There are four aspects to leprosy pathogenesis: spectrum of immune response, bacterial load, nerve damage and immune mediated reactions.

M.leprae multiplies best in cooler parts of the body, so that the skin of the face and limbs and the more superficial nerves are preferentially invaded. The bacilli are taken up by macrophages: histiocytes in the skin and Schwann cells in the nerves where they preferentially multiply. This usually elicits an inflammatory response of histiocytes and lymphocytes. Clinically there is a small vague macule, called "indeterminate" leprosy. Most indeterminate lesions will heal spontaneously. However, if the bacillary growth outstrips the defence mechanisms or the defence mechanism fails, then the condition progresses into one of the patterns that make up

the spectrum of disease. The clinical pattern and ultimate outcome of the disease depend on the nature and extent of the host's immune response and upon the extent of bacillary multiplication (Job, 1994).

When cell mediated immunity is well developed, the pattern of disease is that of tuberculoid leprosy. The disease is localized to one or few sites in the skin and a few large peripheral nerves. Granulomatous inflammation associated with infiltration and destruction of nerve fibres is characteristic. If cell mediated immunity fails to develop the pattern of disease is that of lepromatous leprosy. The clinical picture reflects the heavy bacterial growth in both skin and nerves. In the skin, macrophages fail to differentiate and become sacs filled with acid-fast bacilli (globi) and their cytoplasm undergoes fatty changes and becomes oedematous, giving them the appearance of 'foam' cells. Lymphocytes are absent or scanty and there is no attempt to surround macrophages. Large numbers of bacilli are present in Schwann cells of cutaneous nerve fibres. Schwann cells reduplicate in an attempt to repair the damage and may form concentric rings around the nerve fibre, creating an 'onion skin' appearance on histological sections. Clinically the disease is characterised by multiple lesions all over the body, which progress to nodules. Nasal mucosa is infiltrated early. Involvement of nerve is symmetrical with loss of sensation occurring first, followed by motor damage. Lepromatous leprosy is a systemic disease with multiple organ involvement. Acid-fast bacilli are present in all skin and nerve lesions but can also be found in eyes, bone, muscle, liver, spleen, kidneys and lymph nodes (Job, 1994).

In between the two polar forms lies the rest of the spectrum of disease in leprosy. Histologically, macrophages differentiate into epithelioid cells, but acid-fast bacilli are readily seen within them. Lymphocytes are usually present. The formation of small granulomas is characteristic of borderline leprosy. The granulomas become more diffuse from borderline tuberculoid to borderline lepromatous disease, as the number of bacilli increase. The clinical features reflect the lack of focalization of the disease with many skin lesions of all shapes and sizes and many nerves involved, though not symmetrically as in lepromatous leprosy (Bryceson & Pfaltzgraff, 1990).

The pathology of peripheral nerves associated with leprosy starts distally and affects more proximal nerves as it progresses. *M.leprae* infects both Schwann cells and intra-neural macrophages. The influx of inflammatory cells in the epineurium and

sheaths causes compression within the sheath so that Schwann cells and axons are destroyed. The dead Schwann cells and axons are replaced by fibrous tissue (Scollard, 2008). Further de-myelination occurs through immunological reactions. Although a lot remains unknown in the mechanism of nerve injury in leprosy, inflammation plays an important role in the neurological damage that leads to subsequent tissue damage and eventual deformity.

Phagocytosis of bacilli by other nearby Schwann cells may spread the infection along the nerve. A recent study (Masaki *et al.*, 2013) suggests that *M.leprae* may re-programme Schwann cells genes making infected cells highly plastic, migratory and immune-modulatory. Bacterial spread would then be explained by direct differentiation into mesenchymal tissues and formation of granuloma-like structures and subsequent release of bacteria-laden macrophages.

2.1.5 Immunology of leprosy

Immunological response determines the type of clinical leprosy in a patient. In tuberculoid leprosy, cellular immunity is well developed, whereas in lepromatous leprosy humoral immunity predominates.

Phagocytosis of *M.leprae* by macrophages and dendritic cells is facilitated by C3 receptors present on these cells binding to phenolic glycolipid 1 (PGL-I), an *M.leprae* specific cell wall lipid. In the phagosome, *M.leprae* evades immune surveillance mechanisms, and in individuals with lepromatous leprosy is able to proliferate in a lipid-rich environment. The survival of *M.leprae* within the macrophages is facilitated by components of the cell wall which inhibit the macrophage's inherent killing mechanisms such as oxidative stress. After uptake in macrophages followed by intracellular multiplication, some antigens of *M.leprae* are processed and presented as peptides in the groove of HLA class II molecules on the macrophage surface to induce T cell activation and proliferation. Inflammatory cytokines are released which further activate macrophages resulting in increased resistance to infection. It is uncertain whether this mechanism is effective in Schwann cells.

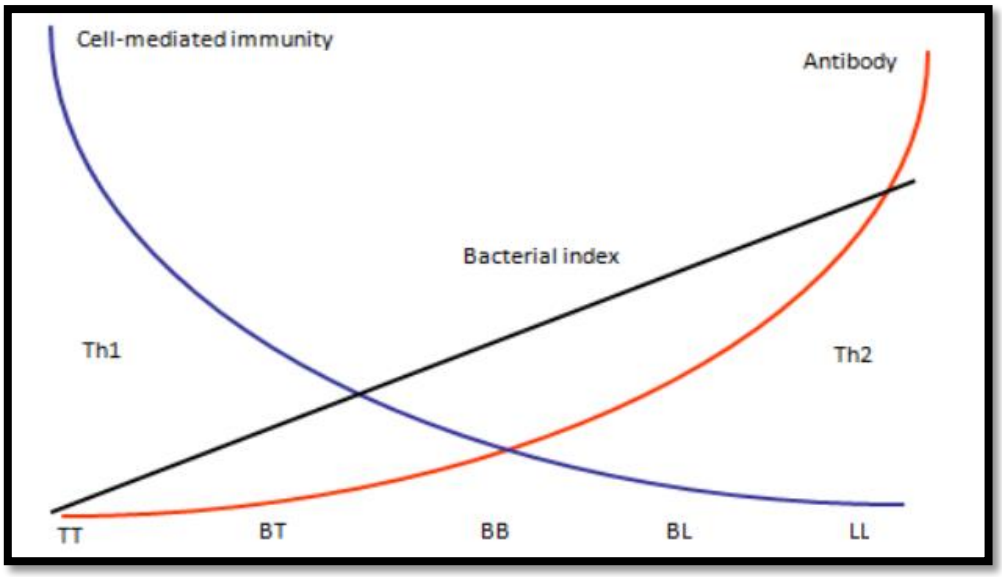
Cell mediated immunity (CMI) in leprosy depends on HLA-DR II molecules presenting *M.leprae* antigen which are then recognized by regulatory T-lymphocytes (T helper cells, Th) and some T-suppressor cells (Ts). These Th (CD4) cells, driven by interleukin 2, secrete interferon-γ which inhibit the migration of macrophages, thus playing a part in the focalization of the lesion, and enabling the macrophages to kill and digest organisms. T cytotoxic cells (Tc or CD8) secrete lymphotoxins which destroy the antigen bearing cells. Tuberculoid lesions contain predominantly the CD4+ helper (inducer) subset, whereas lepromatous lesions contain mainly CD8+ suppressor (cytotoxic) subset in a proportion quite distinct from the normal peripheral blood CD4+/CD8+ ratio (Bach *et al.*, 1983). Macrophages under the influence of cytokines, particularly TNFα together with lymphocytes form granulomas. CD4+ cells are found mainly within the granuloma and CD8 cytotoxic T cells in the mantle area surrounding it (Modlin *et al.*, 1988). Lepromatous disease is characterised by poor granuloma formation.

Humoral immunity is antibody mediated. Antibody combines with antigen and forms complexes to which complement is fixed and then attracts polymorphonuclear leucocytes which accumulate, phagocytose the complexes and release enzymes which can cause tissue damage.

The polar forms of leprosy conform to an immunological paradigm (Walker & Lockwood, 2006a). Tuberculoid leprosy is the result of high CMI with a largely Th1 type immune response and none or very few organisms in the skin or nerves. Lepromatous leprosy however is characterised by an anergic response to *M.leprae*, which is often accompanied by a humoral Th2 response (Modlin, 1994). This lower CMI is associated with large numbers of proliferating bacilli. The dichotomous Th1/Th2 model is not able to precisely explain this important aspect of the immunology of leprosy. The borderline part of the spectrum is immunologically dynamic and movement between the two polar forms occurs (Figure 2.2). These shifts in the immunological response underlie the reactions that are a feature of the borderline states.

M.leprae specific antibodies are usually absent or present at very low levels in tuberculoid leprosy patients. In contrast, lepromatous leprosy patients have numerous skin lesions containing high numbers of bacilli and antibodies of the IgA, IgG and

IgM subtypes are detectable in high titres. But these antibodies show specific immunological unresponsiveness to antigens of *M.leprae* in vivo and in vitro (Ridley & Jopling, 1966; Modlin *et al.*, 1986). The role of specific antibodies directed against *M.leprae* in the pathogenesis of leprosy is unclear.



TT= Tuberculoid, BT= Borderline Tuberculoid, BB= Borderline Borderline, BL= Borderline Lepromatous, LL= Lepromatous

Figure 2.2 Ridley-Jopling classification and features of the host immune response

The balance and complex interaction of cytokines, chemokines, adhesion molecules, their receptors and the cells of the innate and adaptive immune system all play a role in ultimately determining the particular immune response of the individual to the organism and the resultant immunopathology (Walker & Lockwood, 2006b).

2.1.6 Clinical features

Patients commonly present with skin lesions, weakness, numbness and deformity due to a peripheral nerve lesion or with a burn or ulcer in an anaesthetic hand or foot. A leprosy reaction may be the presenting feature.

Cutaneous features

The early skin lesions of indeterminate leprosy are rather poorly defined hypo-pigmented or erythematous macules in which sensation may be unaltered. Macules and plaques with well-defined edges are characteristic of tuberculoid leprosy (TT). There may be a single or very few lesions, most commonly found distributed asymmetrically on the face, extensor surface of the limbs, buttocks or trunk. In dark skin, hypo-pigmentation predominates over the erythema or copper colour more usually seen in lighter skin. The lesions are frequently anaesthetic. The anaesthesia is due to destruction of dermal nerve fibres. Involvement of autonomic fibres is often marked and results in dry lesions with a tendency to scale due to loss of sweating. Hairs are reduced in number or may be completely absent. The TT form carries a good prognosis and lesions will often self-heal.

Borderline tuberculoid leprosy (BT) lesions are similar to those found in TT leprosy but are larger and more numerous, with less pronounced margins and less infiltration (Figure 2.3).

In borderline (BB) leprosy, macular, papular or plaque-like skin lesions including a combination of these can occur. Lesions may have a geographic appearance and some lesions have an ill-defined outer margin with a well-defined ("punched-out") inner margin.

Patients with borderline lepromatous (BL) leprosy usually develop a few macular lesions which become more widespread and symmetrically distributed. The macules become progressively more infiltrated. Papular and nodular lesions may develop and are more defined than those seen in lepromatous leprosy (LL). Skin lesions at the lepromatous (BL/LL) end of the spectrum may not have demonstrable sensory loss.

Lepromatous disease may be present for many years before diagnosis. The early skin changes are widely and symmetrically distributed macules. Flesh coloured or occasionally erythematous papules and nodules may be present. The skin, if left untreated, thickens due to dermal infiltration giving rise to "leonine facies" (Figure 2.4). Hair is lost from affected skin notably from eyelashes and eyebrows (madarosis).

Figure 2.3 Extensive BT lesions on 14 year old Ethiopian

Figure 2.4 A man with lepromatous leprosy

In this 25 year old man with lepromatous leprosy (right), the skin is heavily infiltrated and multiple nodules are present, giving a leonine appearance. Partial madarosis and nodules on the ears are present. He is pictured with his 45 year old uncle.

Neural features

Enlarged peripheral nerves in leprosy are caused by bacillary invasion and subsequent inflammation. In a cohort of multibacillary leprosy patients in Ethiopia, 84% of new cases had at least one thickened nerve, with the ulnar nerve most commonly involved. Up to 55% had some degree of impairment at diagnosis with ulnar and posterior tibial nerves being the most frequently affected peripheral nerves (Saunderson *et al.*, 2000d). Other nerves affected by the disease include the greater auricular, median, radial, radial cutaneous and the lateral popliteal nerves. The presence of a skin lesion overlying a major nerve trunk is associated with a significantly increased risk of impairment in that nerve (van Brakel *et al.*, 2005a).

Figure 2.5 Cervical nerve enlargement
An unusual cord-like cervical nerve with an erythematous lesion on the chin

Nerve involvement in leprosy affects sensory, motor and autonomic function of peripheral nerves. Small dermal sensory nerves are affected producing anaesthesia in the lesions. In tuberculoid leprosy, damage to peripheral nerves is limited, and sensory loss is localised to areas supplied by affected nerves. In lepromatous the destruction of dermal nerves leads to a glove and stocking neuropathy; peripheral nerve involvement tends to occur late and is usually symmetrical. Sensory loss is the earliest and most frequently affected modality. Although many patients may not complain of numbness in hands and feet, painless ulcers in feet and infected burns and cuts on hands are common findings at diagnosis. Motor weakness may be slow

in onset or sudden. In borderline and tuberculoid leprosy, damage to a large peripheral nerve may be gradual and weakness may occasionally present before anaesthesia is noticed. Some patients with BT leprosy can have rapid nerve trunk damage. In lepromatous leprosy nerves are affected late in the disease but a more generalized weakness in hands, feet and face occurs. Autonomic nerve involvement results in anhidrosis, not only in skin lesion but also in the hands and feet supplied by affected nerves. Dryness in hands and feet leads to fissuring and ulceration, putting patients at risk of infections.

Pure neural leprosy (PNL), without any evident skin involvement, manifests with sensory or motor impairment and accounts for about 5% of all cases in India (Mahajan *et al.*, 1996). The prevalence of PNL in an Ethiopian cohort was 0.5% (Saunderson *et al.*, 2000d). Tenderness in enlarged nerves may be present in leprosy especially when entrapment within fibro-osseous tunnels occurs. In leprosy reactions, the nerve may suddenly become oedematous due to inflammation, giving little time for the perineurium to expand. The tight perineurium causes intraneural ischemia, and transient nerve function impairment accompanied by nerve tenderness.

Neuritis is present if an individual has spontaneous nerve pain, paraesthesia, tenderness and/or new sensory or motor impairment (van Brakel *et al.*, 2005a). Neuritis indicates inflammation in the nerve. Nerve pain, paraesthesia or tenderness may precede nerve function impairment (NFI), which, if not treated rapidly and adequately becomes permanent. When nerve function impairment occurs in the absence of painful nerves, it is described as "Silent Neuropathy" (van Brakel & Khawas, 1994b) or "silent neuritis" (Duncan & Pearson, 1982). It is therefore only detected if health workers perform a careful examination of the peripheral nervous system. In Nepal 13% of patients developed silent neuropathy, including 6.8% of new patients who presented with NFI. The majority of silent neuropathy was present at diagnosis or developed during the first year of MDT (van Brakel & Khawas, 1994b). The BANDS investigators reported a cumulative incidence of silent neuropathy of 28% in MB cases after five years follow-up (Richardus *et al.*, 2004). Silent neuropathy can occur in isolation from other types of reaction but may precede or be preceded by T1R (van Brakel & Khawas, 1994b).

Ophthalmological features

A cohort study found that 2.8% of multibacillary patients were blind at diagnosis and 11% had potentially blinding pathology at presentation (Ffytche, 1998; Courtright *et al.*, 2002). Leprosy compromises the eye through nerve damage and by inflammation due to direct bacillary invasion of the skin or eye itself. These factors can occur in combination and result in the four main causes of visual loss: lagophthalmos, corneal ulceration, acute or chronic uveitis and secondary cataract.

Lagophthalmos results from damage to the zygomatic and temporal branches of the facial (VII^{th}) nerve (Figure 2.6). Facial lesions are associated with a ten-fold increase in the risk of facial nerve damage (Hogeweg *et al.*, 1991). In lepromatous disease lagophthalmos occurs later and is bilateral in most cases. Damage to the ophthalmic branch of the trigeminal (V^{th}) nerve causes anaesthesia of the cornea and conjunctiva, leading to drying of the cornea and reduction in blinking. These, in conjunction with the inability to close the eye normally, put the cornea at risk of minor trauma and ulceration.

Bacillary invasion of the iris and ciliary body makes them extremely susceptible to reactions. Uveitis, often affecting the anterior chamber of the eye, is frequently observed in patients with Erythema Nodosum Leprosum and may have an acute or chronic course. Cataracts and glaucoma, secondary to steroid use or due to chronic inflammatory processes are also seen.

Blindness can have devastating consequences for those who may already have sensory loss of the hands and feet.

Nasal features

Involvement of the nasal mucosa in lepromatous leprosy gives rise to nasal stuffiness, and epistaxis may occur in advanced disease (Barton, 1976). Infiltration of nasal structures may lead to a saddle deformity due to septal perforation and destruction of the anterior nasal spine (Figure 2.7). Nasal deformity contributes significantly to the stigma associated with leprosy (Schwarz & Macdonald, 2004).

Figure 2.6 Young girl with bilateral lagophthalmos and right facial nerve palsy

Figure 2.7 Young girl with lepromatous leprosy
Early nasal bridge collapse is seen, as well as a lepromatous nodule in the nostril

Other features

The involvement of other systems as seen in lepromatous disease is due to bacillary infiltration of structures and organs. *M.leprae* is found in lymph nodes, bone marrow, liver, spleen, kidneys and adrenal glands. The lungs do not appear to be affected (Chinen *et al.*, 1997).

Testicular atrophy and azoospermia result from bacillary infiltration in lepromatous leprosy as well as from acute orchitis in ENL. In a small study of 30 Indian patients with BL and LL leprosy, 30% had reduced testicular volume and 10% had gynaecomastia (Abraham *et al.*, 1990b). In another study of 30 patients with BL/LL

leprosy, 10% were found to have demonstrable acid-fast bacilli in their semen (Abraham *et al.*, 1990a).

Osteoporosis in the phalanges of the hands and feet can occur in lepromatous leprosy, predisposing to compression fractures and swelling of the joints. These changes can produce shortening of the digits (Bryceson & Pfaltzgraff, 1990).

2.1.7 Differential Diagnosis

The diagnosis of leprosy should be made positively, and not by exclusion or by therapeutic trial. The manifestations of leprosy are variable and it can mimic a great variety of other conditions. Local artefacts due to traditional practices or local cosmetic practices should always be considered. Complete loss of pigment such as in vitiligo is never due to leprosy. The hypo-pigmented lesions of pityriasis alba in children can be difficult to distinguish from early disease. Fungal infections such as pityriasis versicolor, tinea corporis and tinea faceii commonly mimic leprosy, and may cause diagnostic difficulty when the lesions are erythematous plaques. Other granulomatous conditions such as sarcoid, granuloma multiforme, cutaneous tuberculosis and granuloma annulare may resemble leprosy. Patients with cutaneous leishmania are often referred to the leprosy clinic in Ethiopia. In countries where *Leishmania donovani* is endemic, post-kala-azar dermal leishmaniasis is a differential diagnosis in lepromatous leprosy. The lesions of cutaneous T cell lymphoma may also mimic borderline types of leprosy. Nodular syphilis can be mistaken for lepromatous leprosy (Dupnik *et al.*, 2012). In all of these conditions, the peripheral nerves are spared, and histological examination is helpful.

Nerve thickening is a feature of rare neurological conditions such as hereditary sensory motor neuropathy Type III and Refsum's disease. Amyloidosis, which itself can complicate leprosy, can cause nerve thickening.

Late diagnosis in leprosy because of misdiagnosis is common. In many low resource settings, where health staff with knowledge of leprosy are few, patients are often misdiagnosed. Late presentation can also be related to the stigma attached with leprosy and the attempt to hide the diagnosis or to the lack of awareness and access to medical services (Nicholls *et al.*, 2005; Bekri *et al.*, 1998). In non-endemic areas,

the diagnosis is frequently delayed because leprosy is not considered and patients present to a wide range of specialists (Lockwood & Reid, 2001).

2.1.8 Diagnosis and Investigations

The diagnosis of leprosy is essentially a clinical one, based on finding one or more of the cardinal signs of leprosy (Table 2.1) (WHO, 2012b).

Cardinal Signs of leprosy
- Definite loss of sensation in a pale (hypo-pigmented) or reddish skin patch
- Thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve
- Presence of acid-fast bacilli in a slit-skin smear.

Table 2.1 Cardinal signs of leprosy

The cardinal signs elicited by clinical examination are variable in their sensitivity and specificity. Sensory loss is not a feature of the skin lesions in patients with BL or LL leprosy. In the Ethiopian ALERT MDT Field Evaluation Study (AMFES) sensory loss in skin lesions was present in 70% of the 594 individuals with leprosy (Saunderson & Groenen, 2000). In a population survey in Karonga district in Malawi, anaesthesia was found in only 48.5% of leprosy skin lesions confirmed by histopathology (Ponnighaus & Fine, 1988). The majority of the Malawians found to have leprosy had TT/BT leprosy.

Slit-skin smear test: The slit-skin smear test is the most simple and frequently used laboratory method to identify acid fast *M.leprae*. The Bacillary Index (BI) is a logarithmic scale (1-6) quantifying the density of M.*leprae* on a slit-skin smear. From a cross-sectional study in India, slit-skin smear test confirmed the presence of acid-fast bacilli in 59.8% (64/107) of multibacillary and only in 1.8% (1/57) of

paucibacillary cases (Banerjee *et al.*, 2011). In the Ethiopian AMFES cohort, 55% of individuals with multibacillary leprosy had a negative slit-skin smear (Saunderson *et al.*, 2000c). A recent correlation study between clinical classification and slit-skin smear confirmed that the investigation has high specificity but low sensitivity (Santos *et al.*, 2013). Slit-skin smears are now mainly done in referral centres and are useful in confirming the diagnosis of leprosy and monitoring the response to treatment. A negative result does not rule out leprosy.

Skin biopsy: The histological examination of a skin biopsy is the gold standard for diagnosis of leprosy. The presence of granulomata and lymphocytic infiltration of dermal nerves in anaesthetic skin lesions confirms the diagnosis. Occasionally a nerve biopsy may be needed to confirm the diagnosis. A nerve biopsy is performed on a purely sensory nerve (e.g. radial cutaneous or sural nerve). Leprosy classification was changed after histopathological analysis in up to 20.2% of patients in a Brazilian study (Santos *et al.*, 2013) whereas in the INFIR cohort, 41% of BT and 46% of LL cases had to be re-classified (Lockwood *et al.*, 2012b). Histopathological evaluation is essential for accurate classification of leprosy lesions and is the best diagnostic test in a well-resourced setting, both for confirming and for excluding the diagnosis of leprosy.

Serological tests: The lateral flow test detects anti-PGL-1 antibodies in the serum of leprosy patients. This may be useful as an additional tool for classifying but not diagnosing leprosy (Oskam *et al.*, 2003). The test is not sensitive in individuals with PB disease as only 15-40% of these patients have detectable antibodies. A new diagnostic test for leprosy by Orange Life, detecting anti-PGL-1 antibodies and a fusion of two protein antigens (LID) is currently being promoted as an early test for leprosy (McNeil, 2013). In Venezuela, patients across the Ridley-Jopling spectrum tested sero-positive for LID, with rates of 97% for LL patients, 96.4 % for BL and 76.9 % for BB. The figures for BT and TT sero-positivity are not given but appear to be low and zero for BT and TT patients respectively (Duthie *et al.*, 2011). This new test may have good sensitivity in early lepromatous leprosy but low sensitivity in patients with tuberculoid leprosy, and its value as a diagnostic test for early leprosy may be questionable. It might in fact contribute to delayed diagnosis in patients on the tuberculoid end of the spectrum, as health staff might be erroneously guided by false negative results.

Molecular based diagnosis: Following the sequencing of the *M.leprae* genome, PCR based diagnosis of leprosy has become possible. A study comparing real time and conventional PCR for detecting *M.leprae* DNA in 69 biopsy samples from Brazilian patients reported clinical sensitivity as 91.3% and 82.6% respectively. The detection rate of *M.leprae* DNA was 100% among multibacillary patients and 62.5% to 79.2% among paucibacillary patients. The study also detected *M.leprae* DNA in five out of the six skin biopsies of patients with pure neural leprosy (no skin lesion) (Martinez *et al.*, 2006). Another study conducted in India, showed that 85.9% of multibacillary patients and 75.5% of paucibacillary patients had positive *M.leprae* PCR on skin biopsy (Banerjee *et al.*, 2011). Although PCR increases the sensitivity of *M.leprae* DNA detection, satisfactory results are yet to be achieved with regard to the detection of early paucibacillary cases as shown above. PCR may also detect carriers of *M.leprae* DNA with no active disease. Molecular tools such as PCR are potentially highly specific and sensitive, but their uses in the diagnosis of leprosy have been confined to high-income settings and research centres.

2.1.9 Classification of leprosy

Classification of leprosy is not only important in determining prognosis and appropriate treatment; but also helps to identify those patients at risk of complications and those at risk of transmitting the disease. There are two systems used to classify leprosy patients.

The Ridley-Jopling Classification (Ridley & Jopling, 1966) was developed to correlate clinical and histopathological findings in leprosy. It assists the understanding of the disease and is usually used in research settings. The system uses bacteriological index as well as clinical and histopathological features to classify patients (Table 2.2). Leprosy patients are categorised into a spectrum with polar tuberculoid (TT) and lepromatous (LL) forms and middle types of borderline tuberculoid (BT), borderline borderline (BB) and borderline lepromatous (BL) leprosy. Patients in the borderline states are immunologically unstable and at risk of reactions.

Classification					
Ridley-Jopling	**TT**	**BT**	**BB**	**BL**	**LL**
WHO	**PB**	**PB/MB**	**MB**	**MB**	**MB**
Clinical features					
Skin					
Infiltrated lesions	Defined plaques, Healing centres	Irregular plaques Partially raised edges,	Polymorphic 'Punched out centres'	Papules, nodules	Diffuse thickening
Macular lesions	Single, small 'Geographic'	Several, any size, Bizarre	Multiple, all sizes	Innumerable, small confluent	Innumerable
Hair growth	Absent	Markedly diminished	Moderately	Slightly diminished	Minimally diminished*
Nerve					
Peripheral nerve	Solitary, enlarged	Several nerves	Many nerves	Late neural thickening	Widespread thickening
Nerve function impairement	None	Asymmetrical	Asymmetrical pattern	Asymmetrical anaesthesia and paresis	Glove and stocking anaesthesia
Systemic features					
	None	None	None	Some	Nasal stuffiness, epistaxis. Testicular atrophy. Ocular involvement. Bones & internal organs can be affected.
Microbiology					
Bacterial index	0–1	0–2	2–3	1–4	4–6
Histology					
Lymphocytes	1	11	1/2	11	1/2
Macrophages	2	2	1/2	2	2
Epithelioid cells	11	1/2	2	2	2
Antibody, anti-*M.leprae*	2/1	2/11	1	11	11

(In advanced disease, almost all body hair is lost).*

Table 2.2 Characteristics of the Ridley-Jopling Classification *modified from Medicine in Africa: Leprosy* (Lockwood *et al.*, 2012a)

The WHO classification is a simplified version which can be used in the field even when slit-skin smears are not available. It relies on the number of lesions on the patient (Table 2.3). If a skin smear is done and is positive, the patient must be classified as MB, whatever the number of lesions. This is a quick and useful tool which can be employed by a wide variety of health care workers as it provides a low cost strategy for leprosy diagnosis, without the need for skilled clinical assessment and slit skin smear examination. It is mainly used to guide length of treatment (WHO, 2006).

LEPROSY TYPE	NUMBER OF SKIN LESIONS
Paucibacillary (PB)	1–5
Multibacillary (MB)	6 or more

Table 2.3 WHO operational classification of leprosy

One of the main limitations of the WHO classification is that by concentrating on skin lesions, it misses out on patients with pure neural leprosy. The loss of neurological assessment skills in health workers increases the risk of disability in patients.

The MB group as it is currently defined is very heterogeneous. It includes some individuals with BT leprosy and all those with BB, BL and LL. In the INFIR study approximately 60% of the cohort of MB patients had a negative bacterial index (BI) (van Brakel *et al.*, 2005a). A similar figure of 63.29% was reported for the BANDS cohort (Croft *et al.*, 1999).

The Ridley-Jopling classification is the recommended classification system for use in studies examining immunological processes or genetic susceptibility to leprosy or leprosy complications (Lockwood *et al.*, 2007).

2.1.10 Nerve function assessment

Nerve involvement is important in leprosy. It is vital to check nerve function at every clinic visit so that loss of function can be detected early. The first step in nerve function assessment is a detailed history followed by gentle palpation of the nerves at specific sites to assess for enlargement and tenderness (Figure 2.8).

The assessment of nerve function is done by testing voluntary muscle function (VMT) and sensation (ST) in the face, hands and feet.

Motor function

The motor function of individual nerves is assessed by testing the power in the small muscles of the hands and feet which they innervate (Table 2.4). It is important to ensure that the muscle being tested is isolated by careful positioning.

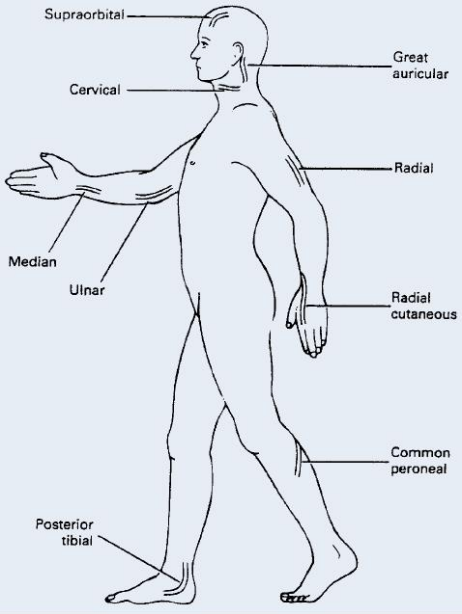


Figure 2.8 Nerves examined by palpation in leprosy

Nerve tested	***Muscle***	***Movement tested***
Facial nerve	orbicularis oculi	Forced eye closure
Median nerve	abductor pollicis brevis	Thumb abduction
Ulnar nerve	abductor digiti minimi	Little finger abduction
Radial nerve	extensor muscles	Wrist extension
Lateral popliteal nerve	tibialis anterior, peroneus longus and brevis	Foot dorsiflexion
Posterior tibial nerve	intrinsic muscles of foot	Great toe grip

Table 2.4 Commonly tested nerves and muscles in motor function assessment

Motor function is graded by using the six grades on the Medical Research Council (MRC) scale for muscle power (Table 2.5)(MRC, 1981).

MRC modified grading of muscle power	
Score	Muscle response
5	Full range of movement (FROM)
4	FROM but less than normal resistance
3	FROM but no resistance
2	Partial range of movement with no resistance
1	Perceptible contraction of the muscle not resulting in joint movement
0	Complete paralysis

Table 2.5 MRC scale for VMT

In the ILEP Nerve Function Impairment and Reaction ('INFIR') Cohort Study in India, the concordance between VMT results and motor nerve conduction was good for the ulnar nerve, but very few median and peroneal nerves with abnormal conduction had an abnormal VMT (van Brakel *et al.*, 2005a)

Sensory function

The method of sensory testing used depends on the availability of equipment and personnel trained to use it. The use of a ball-point pen at four sites on each hand and foot is recommended in the Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities (2006-2010) (WHO, 2006). The ball-point pen is used to gently depress the skin such that a dimple of approximately 1 cm across is created at each test site. The ball-point pen test has been shown to have good inter-observer reliability (Anderson & Croft, 1999).

Semmes-Weinstein monofilaments (SWM) are able to detect more subtle loss than the ball-point pen (Koelewijn *et al.*, 2003) but require more training of personnel and are less widely available. SWM are standardised graded nylon filaments attached to a handle. The stimulus is applied to the test site until the thread just bends (Figure 2.9) and the patient is asked to indicate where they felt the stimulus (Brandsma, 1981). Three test points are used for each nerve (median and ulnar) in the hand and four for the posterior tibial nerve on the foot (Figure 2.9).The graded weights used in leprosy studies are 200mg, 2g, 4g, 10g and 300g. SWM are very reliable when used by trained personnel (Anderson & Croft, 1999). The level of agreement was high but it is important to ensure that training is regularly repeated and inconsistencies associated with technique are corrected (Roberts *et al.*, 2007). SWM have been shown to have good concordance with sensory nerve conduction and quantitative sensory testing such as thermal thresholds but are less sensitive (van Brakel *et al.*, 2005b). In the INFIR cohort study, during a two year follow-up, up to 50% of 188 MB patients developed subclinical neuropathy that was not evident when only SWM and VMT were used. Sensory nerve conduction and warm detection thresholds preceded SWM and VMT deterioration by up 12 weeks or more, indicating that these tests could improve early detection of neuropathy (van Brakel *et al.*, 2008).

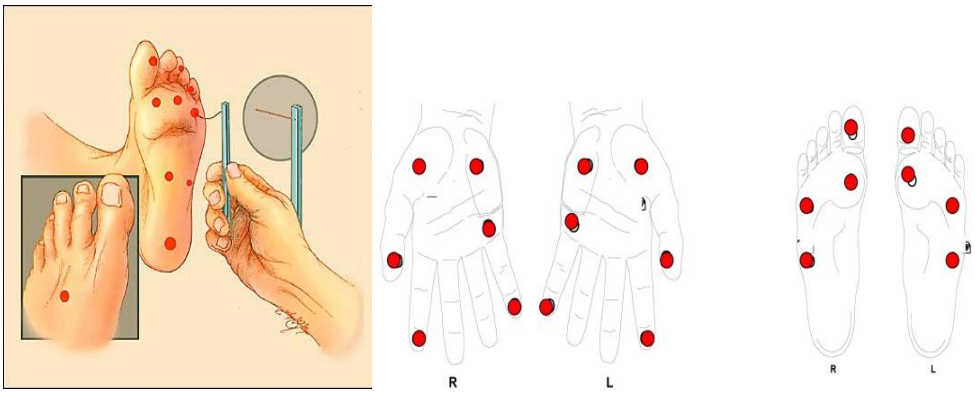


Figure 2.9 Filament testing for sensation and standard testing points

2.1.11 Disability grading

The disabilities caused by nerve damage in leprosy affect mainly the hands, feet and eyes. The WHO disability grading of these impairments can assist in providing appropriate care and prevent further disability (Table 2.6) (WHO, 1988).

WHO Grade	0	1	2
Eyes	Normal	-	Reduced vision (unable to count fingers at 6 metres). Lagophthalmos.
Hands	Normal	Loss of feeling in the palm of the hand	Visible damage to the hands, such as wounds, claw hands or loss of tissue.
Feet	Normal	Loss of feeling in the sole of the foot	Visible damage to the foot, such as wounds, loss of tissue or foot drop.

Table 2.6 WHO Disability Grading

In the INFIR cohort, 40.9% of the newly diagnosed Indian patients had WHO disability grade-1 and 9.6% grade-2 at enrolment (van Brakel *et al.*, 2005a). The BANDS cohort had a prevalence of grade-1 and grade-2 disability of 9.61% and 5.97% overall (PB and MB patients) at enrolment. However the rate of grade-1 disability was 28.48% and grade-2 18.24% in the MB patients (Croft *et al.*, 1999). The proportion of grade-2 disability in newly diagnosed leprosy cases in 2011, varied between India (3%) and China (27%) (WHO, 2012a). Although this is dependent on accurate reporting, the reduction of new cases with grade-2 disabilities

is one of the new indices for successful leprosy burden reduction as well as a marker of early diagnosis (WHO, 2009a).

2.1.12 Treatment of M.leprae infection

A successful treatment for leprosy was only discovered in 1947 with dapsone, which remains a component of present day WHO recommended multi-drug combination.

Dapsone

Dapsone is bacteriostatic and effective against a wide range of bacteria and protozoa. In 1947, Cochrane used 1.25 g of subcutaneous dapsone twice weekly to successfully treat leprosy patients (Cochrane RG, Ramanujam K, Paul H, 1949). By 1951, the standard treatment for leprosy was oral dapsone, 100mg daily, and was used widely as monotherapy in the 1950s and 1960s. A dose of 100mg of dapsone is weakly bactericidal against *M.leprae* and after a few weeks of starting dapsone therapy active lesions start to improve. However, in the late 1960s two important problems developed: firstly, "secondary resistance" or relapse in patients who had previously been treated with dapsone was identified, then "primary resistance" in patients who had never been exposed to dapsone.

The WHO reports that side effects are rare with dapsone. A retrospective study of 194 Brazilian patients found that 43% experienced adverse effects attributed to dapsone (Deps *et al.*, 2007). Dapsone causes haemolysis, which may be severe especially in individuals with glucose-6-dehydrogenase deficiency (Degowin *et al.*, 1966). Dapsone hypersensitivity usually starts 3–6 weeks after starting the drug, with fever, pruritus and a dermatitic rash. Unless dapsone is stopped immediately, the syndrome may progress to exfoliative dermatitis. Hepatitis, albuminuria, psychosis and death have also been recorded (Lowe & Smith, 1949; Pandey *et al.*, 2007). Treatment involves stopping dapsone and treating with corticosteroids for several weeks. The incidence of dapsone hypersensitivity is estimated at one per several hundred patients, but appears to be higher (0.5%-3.6%) in Chinese patients. A Chinese study of 39 patients who developed dapsone hypersensitivity out of 872 treated with dapsone as part of MDT, found that the presence of the HLA-B*13:01 gene was highly predictive of dapsone hypersensitivity (Zhang *et al.*, 2013).

Although dapsone-induced peripheral neuropathy has been reported in some diseases there have been few reports of it occurring in leprosy.

Clofazimine

Clofazimine was first used for the treatment of leprosy as monotherapy in the early 1960s and continued until the mid-1970s. To date there has been only one reported case of resistance (Warndorff-van Diepen, 1982). Clofazimine is bacteriostatic and slowly bactericidal against *M.leprae*, similar to dapsone (Levy *et al.*, 1972), but the mechanism of its action against *M.leprae* is unknown. At doses greater than 1 mg/kg daily clofazimine exhibits increasing anti-inflammatory activity. Clofazimine is lipophilic and is therefore deposited in fatty tissue and cells of the reticulo-endothelial system. Autopsies carried out on patients who had been on clofazimine therapy revealed large quantities of the drug in mesenteric lymph nodes, adrenal glands, subcutaneous fat, liver, spleen, small intestine and skin but not in the central nervous system (Mansfield, 1974).

The main problems encountered with clofazimine are increased skin pigmentation and dryness (ichthyosis), which occur as the drug becomes clinically effective (Jopling, 1976). Pigmentation can also be seen in the cornea as well as conjunctival and macular areas of the eyes. This unpleasant effect may make the drug unacceptable to some patients particularly if cosmetically sensitive sites are affected. The discoloration fades slowly on withdrawal of the drug, as does the ichthyosis on the shin and forearms. Clofazimine crystals may be deposited in the bowel and can cause an enteropathy (Atkinson *et al.*, 1967).

Rifampicin

Rifampicin is the only strongly bacteriocidal anti-leprosy drug, which renders the patient non-infectious within days of commencing therapy (Levy *et al.*, 1972). The public health risk posed by lepromatous patients is thought to cease to be significant within a "few" days of starting rifampicin (Waters *et al.*, 1978). As it is the most important component of MDT, there are concerns about the development of drug resistance to rifampicin. Resistance to rifampicin has been shown to be due to tightly clustered mutations in a short region of the rpoβ gene of *M.leprae* (Honore & Cole,

1993). This has led to various rapid PCR based tests which detect mutations linked to drug resistance, and are useful in relapse patients (Cambau *et al.*, 2012).

Few serious side effects have been related to rifampicin, which may be due to its monthly dosing regimen. The most common reported side effect is hepatotoxicity, which has (rarely) resulted in death. Early symptoms are anorexia, vomiting and jaundice associated with a two or threefold increase in hepatic transaminases. The elevated transaminases may be transient and return to normal despite continuing therapy.

'Flu-like' syndrome has been reported with intermittent rifampicin therapy and consists of chills, fever, headache, myalgia and arthralgia. This syndrome has a reported incidence of 0.3% in the WHO/MDT report of complications. Rifampicin also produces a red-brown discoloration of urine, faeces, saliva, sputum, sweat and tears; patients should be informed that this is inconsequential and will last only 24 to 48 hours after ingestion.

MDT

Multi-drug therapy (MDT), a combination of dapsone, rifampicin and clofazimine is the current treatment for infection with *M.leprae* (Table 2.7). Following the emergence of resistance to dapsone-only regimens, the WHO introduced MDT in 1982 (WHO, 1982). Between 1985 and 2005, over 14 million people received MDT. MDT has been very successful, with a high cure rate, few side effects and low relapse rates. The benefits of MDT include the prevention of drug resistance and better patient compliance due to a fixed duration of therapy. Another advantage of MDT is that field workers review patients regularly whilst observing the taking of the monthly supervised dose of MDT.

The WHO reduced the recommended treatment period for MB disease from 24 to 12 months (WHO, 1994), but many advocate 24 months for patients with a BI>4 at diagnosis, especially after studies demonstrated that 90% of relapses occurred in patients with a BI>4 (Girdhar *et al.*, 2000). One option would be to treat such patients until their skin smears are negative or to keep them under regular review. MDT is safe in pregnancy and in breastfeeding mothers. Children receive reduced doses of the drugs.

Type of leprosy	Drug treatment		Duration of treatment
	Monthly, supervised	**Daily, self-administered**	
Paucibacillary	Rifampicin 600mg Dapsone 100mg	Dapsone 100mg	6 months
Multibacillary	Rifampicin 600mg, Clofazimine 300mg Dapsone 100mg	Clofazimine 50mg, Dapsone 100mg	12 months

Table 2.7 WHO-recommended MDT regimens for adults with leprosy

Other regimens instead of MDT

Following the success of MDT there has been research into the use of other drugs that are as effective as MDT, but which require a shorter duration of therapy. Other antibiotics currently available as second-line therapy to MDT are minocycline, ofloxacin, clarithromycin and moxifloxacin (Britton & Lockwood, 2004).

Single-dose therapy

A single-dose MDT is now available for paucibacillary patients: rifampicin 600mg, ofloxacin 400mg and minocycline 100mg (ROM). A recent systematic review has assessed 14 studies comparing ROM and MDT and found that single dose ROM still has a very high cure rate but is slightly less effective than WHO-MDT (relative risk: 0·91; 95% confidence intervals: 0.86-0.97) (Setia *et al.*, 2011). ROM given as a single monthly dose for 24 months was shown in a small Philippines study to be as effective as MDT in the treatment of multibacillary leprosy (Villahermosa *et al.*, 2004). The single monthly dosing might improve compliance and reduce side effects. Larger studies to test the efficacy of monthly ROM are needed (Lockwood & Cunha, 2012).

Relapse in leprosy and drug resistance

Relapse is defined as the re-occurrence of the disease at any time after the completion of a full course of treatment with WHO recommended MDT. Relapse is diagnosed by the appearance of definite new skin lesions and/or an increase in bacteriological index (BI) of two or more units at any single site compared to BI taken from the same site at a previous examination (WHO, 2009b). "Relapse" in leprosy may represent new infection or growth of residual dormant *M.leprae* not killed by MDT, often called "persisters".

The relapse rates following MDT are low. In PB disease reported rates of relapse are between 0.19 and 2.4% (Boerrigter *et al.*, 1991; Chopra *et al.*, 1990). In MB disease the highest reported relapse rate was in 33 out 165 (20%) of 260 Colombian multibacillary patients who were treated with 12 months of MB MDT (Guerrero-Guerrero *et al.*, 2012). In a long-term follow-up study of up to 16 years in the Philippines, the relapse rate amongst MB patients was 6.6% (Balagon *et al.*, 2009). Multi-centre studies using the same criteria for relapse would be useful to evaluate the true extent of the problem (Deepak & Gazzoli, 2012).

Genetic studies have identified mutations within drug target genes in *M.leprae*, which confer resistance to dapsone, rifampicin and ofloxacin. From these studies, drug resistance in *M.leprae* is attributable to chromosomal mutations in genes encoding drug targets. These mutations occur spontaneously as a result of errors in DNA replication and they can be enriched in a population of susceptible *M.leprae* by inappropriate drug therapy. Drug-resistant *M.leprae* mutants can be acquired during initial infection from an infection source containing drug-resistant leprosy (primary drug resistance) or from inadequate treatment (secondary drug resistance)(Williams & Gillis, 2012). A global surveillance of drug resistance in leprosy has been set up by the WHO, using PCR-direct sequencing of drug resistance determining regions of *M.leprae* (WHO, 2009c). During 2010, a total of 109 relapsed cases were diagnosed at sentinel sites, 88 of which were tested for drug resistance. Nine (10%) were resistant to dapsone and one (1.1%) case tested positive for resistance to rifampicin. No multi-drug resistant cases were detected in this cohort (WHO, 2011).

2.1.13 Management of leprosy and prevention of disability

The treatment of leprosy highlights the importance of patient-centred medicine. Education and counselling of the patient and family is as important as chemotherapy. A clear explanation of the disease and refutation of myths about leprosy will help the patient come to terms with the diagnosis and might well improve adherence with treatment (Rao, 2008). The physician should emphasise that gross deformities are not the inevitable end-point of disease, and that care and awareness of the limbs is as important as antibiotics (Britton & Lockwood, 2004). One advantage of supervised MDT is that the monthly visits permit continued education and surveillance for reactions. Monitoring sensation and muscle power in patients' hands, feet and eyes should be part of the routine follow-up, so that nerve damage is detected early. The early detection of deterioration in nerve function and the rapid introduction of corticosteroid therapy are essential to minimise nerve damage and thus prevent disability.

The goal of prevention of disabilities (POD) activities should be the prevention of new disabilities and impairment, but also the prevention of worsening of existing disabilities. Even though evidence for cost effectiveness of POD interventions for leprosy in resource-limited settings is scarce (van Veen *et al.*, 2009b), there is evidence of clinical effectiveness (Ganapati *et al.*, 2003).

The patient's self-awareness is crucial so that damage is minimised. Affected eyes need protection from dust with sunglasses and night cover with eye masks. Dry hands and feet need soaking in water, followed by rubbing with emulsifying ointment. Callus can be rubbed down with pumice and fissures need to be covered to allow them to heal. A patient with an anaesthetic hand or foot needs to understand the importance of protection when undertaking potentially dangerous tasks, and regular inspection for signs of trauma. It has been demonstrated in Nepal that training people in self-care can reduce the requirement for admission to hospital with plantar ulceration (Cross & Newcombe, 2001). Anaesthetic feet need protective footwear, but special shoes are difficult to produce and can increase stigma. A randomised controlled trial of footwear for leprosy patients showed that cheap canvas shoes with cushioned insoles were protective, cost-effective, and preferred to orthopaedic shoes (Seboka & Alert, 1996). Once there is deformity such as clawing,

shoes must be made specifically to ensure protection of pressure points and even weight distribution. Damaged neuropathic areas should be protected from further damage by resting the area and any secondary infection treated with appropriate antibiotics. Surgical intervention may be required to debride necrotic tissue and allow drainage of any collection. Reconstructive surgery may have a role in trying to improve function in cases of contractures, foot drop and lagophthalmos. The role of physiotherapy and occupational therapy is important in preventing contractures as well as in rehabilitation post-surgery. One of the barriers to successful prevention of disability appears to be poor relationships between the patient and health providers at all levels (Cross, 2007).

The stigma associated with the diagnosis of leprosy is still a very real problem and the management of someone with the disease should include discussion of their psychosocial status and education for the patient and their family. Isolation of leprosy patients is of no public health value and in fact increases stigma. The patient may have difficulty in coming to terms with leprosy, and behaviours may vary from concealment, denial to self-isolation. Many communities still isolate leprosy patients.

Education, advocacy and community based development activities are essential in tackling stigma.

2.1.14 Leprosy and pregnancy

The interaction between leprosy and pregnancy is well recognised. The development of T1Rs and neuritis is increased in the postpartum period when cell-mediated immunity returns to the pre-pregnant level (Duncan & Pearson, 1982; Lockwood & Sinha, 1999). ENL reactions occur throughout pregnancy and lactation, and the onset of nerve damage in these patients is earlier than in those who are not pregnant (Duncan & Pearson, 1984). There is little evidence that pregnancy promotes infection or leprosy relapse.

2.1.15 Leprosy and HIV

Early in the HIV pandemic, with increased incidence of mycobacterial diseases such as *M.avium* and *M.tuberculosis,* it was predicted that HIV infection would worsen leprosy outcomes, with more patients developing lepromatous disease and an impaired response to multi-drug therapy (Miller, 1991). With immunity diminished by HIV, fewer reactions were expected. However studies on the epidemiological and clinical aspects of leprosy suggest that the course of leprosy in co-infected patients has not been greatly altered by HIV (Ustianowski *et al.*, 2006).

Higher rates of Type 1 Reactions in MB leprosy patients with HIV have been reported in Ethiopia (Gebre *et al.*, 2000) and in Uganda (Bwire & Kawuma, 1994). Reactions in co-infected patients respond well to steroids (Gebre *et al.*, 2000; Vreeburg, 1992; Bwire & Kawuma, 1994). The adverse effect of additional immunosuppression in HIV positive patients with T1Rs is unknown.

Since the introduction of highly active antiretroviral therapy (HAART) in the management of HIV, especially in regions endemic for leprosy, leprosy is being increasingly reported as part of the Immune Reconstitution Inflammatory Syndrome (IRIS). Initiation of HAART and the associated increase in immunity, has been linked with activation of subclinical M.*leprae* infection and exacerbation of existing leprosy lesions (Lawn *et al.*, 2003; Couppie *et al.*, 2004). T1Rs have been increasingly reported in individuals with HIV co-infection as part of IRIS following the commencement of anti-retroviral therapy (Deps & Lockwood, 2010). There are several possible mechanisms for the pathogenesis of leprosy IRIS. Leprosy has a long incubation period and HAART may provide the immunological trigger of normal disease. Another explanation is that leprosy-associated IRIS is similar to a T1R or that immunosuppression secondary to HIV infection itself causes leprosy reactions.

2.2 LITERATURE REVIEW OF LEPROSY REACTIONS

Leprosy reactions are immunologically mediated episodes of acute or sub-acute inflammation and are the main complication of the disease. They can occur before, during and after successful completion of MDT. The two main types of reaction are Type 1 (Reversal) Reaction and Erythema Nodosum Leprosum (ENL), also known as Type 2 Reaction.

2.2.1 Type 1 Reactions

T1Rs manifest clinically with erythema and oedema of skin lesions and tender peripheral nerves with loss of nerve function.

Epidemiology

There is a large variation in T1R frequency reports in both cohort studies and retrospective studies which may be as a result of different methodologies (Table 2.8).

In Nepal, a retrospective study at a referral centre reported 30.1% of individuals with newly diagnosed leprosy developed T1R (van Brakel *et al.*, 1994). Half of these individuals had demonstrable new nerve function impairment (NFI). In a similar study in Hyderabad, India, T1R was reported amongst 8.9% of 494 patients monitored for six years (Lockwood *et al.*, 1993). Most other retrospective studies report T1R frequency figures between these two.

Prospective studies are more accurate. In the INFIR cohort, 19.8% (60 of 303) had a T1R at recruitment and up to 39% (74 of 188) had experienced a reaction or NFI during the two year follow-up period (van Brakel *et al.*, 2005a). Similarly, 35.7% of a cohort of MB patients in Malawi experienced a T1R or a deficit in nerve function, during a three year period (Pönnighaus & Boerrigter, 1995). In Nepal, 31% of patients with borderline leprosy had a T1R during the first two years of MDT (Roche *et al.*, 1991).

Location of study	Type of study	Number of patients	Type of leprosy	Duration of follow-up (years)	Frequency of Type 1 reactions and/or nerve function impairment (%)
PROSPECTIVE STUDIES					
Vietnam (Ranque *et al.*, 2007)	Referral hospital Case-control study	237	All types except indeterminate	Not clear.	29.1
India (van Brakel *et al.*, 2005b)	INFIR -Referral hospital Cohort study	303	Multibacillary	2	19.8 at diagnosis 39 overall
Bangladesh (Richardus *et al.*, 2004)	BANDS - Referral hospital Cohort study	2664	Paucibacillary and Multibacillary	PB 3 MB 5	PB 0.9 MB 17
Ethiopia (Saunderson *et al.*, 2000a)	AMFES – Field Cohort study	594	New patients	6-11	16.5
Malawi* (Ponnighaus and Boerrigter, 1995)	Randomized trial of MB MDT	305	Multibacillary BI ≥2 at any site	Mean follow-up 3 years	35.7
Thailand (Scollard *et al.*, 1994)	Referral hospital Cohort study	176	All newly diagnosed types	3 min.	19.9
Nepal (Roche et al 1991)	Referral hospital Cohort study	136	Multibacillary-Borderline cases	2	31%
RETROSPECTIVE STUDIES					
Chandigarh, India (Kumar *et al.*, 2004)	Tertiary referral clinic records review	2867	All types except pure neuritic leprosy	3-13	24.1 at diagnosis 33 overall
Orissa, India (Santaram and Porichha, 2004)	Regional leprosy centre records review	942	Patients registered between 1992-2002	Not clear	10.7
Brazil (Nery *et al.*, 1998)	Leprosy clinic records review	162	Untreated slit skin smear positive patients	Not clear	25.9
Nepal (van Brakel *et al.*, 1994)	Leprosy hospital clinic records review	386	Untreated patients except those with pure neuritic leprosy	Mean 1.73	30.1
Hyderabad, India (Lockwood *et al.*, 1993)	Leprosy research centre clinic records review	494	All types	≤6	8.9
Hyderabad, India* (Hogeweg *et al.*, 1991)	Leprosy research centre clinic records review	1226	Paucibacillary (Tuberculoid and borderline tuberculoid 1982-87)	Not clear	24

**These studies used definitions of PB and MB leprosy which differ from the current WHO definitions (modified from table courtesy of Dr Stephen Walker, PhD thesis 2009)*

Table 2.8 Frequency of Type 1 Reactions

A prospective hospital based study from Vietnam demonstrated a prevalence of T1Rs of 29.1% in 337 patients with mainly BB and BL leprosy (Ranque *et al.*, 2007). The AMFES study in Ethiopia, a prospective field study of 594 individuals with up to ten years follow-up, reported a rate of T1Rs of 16.5% (Saunderson *et al.*, 2000b). Hospital or referral centre studies, may be biased compared to field studies, as numbers would be higher in a hospital environment where patients are attending because of reactions and receive close follow-up for signs of reaction.

Risk factors

Although T1Rs can occur at any time, the frequency is higher after starting MDT. The peak time for reversal reactions is the first six months of treatment (Croft 2000). Indian and Ethiopian cohort studies show that patients continue to experience reactions and neuropathy in the third year after diagnosis and beyond (Saunderson *et al.*, 2000b; van Brakel *et al.*, 2008), despite MDT completion. T1R occurring ten years after completion of MDT has been reported (Thacker *et al.*, 1997). The first six month post-partum is also a high risk period for T1R in women with leprosy (Lockwood & Sinha, 1999).

Borderline disease is a major risk factor for developing T1Rs (Ranque *et al.*, 2007). BL and BB patients have a higher risk than BT patients (de Rijk *et al.*, 1994; Lockwood *et al.*, 1993). Small numbers of patients with the polar forms of leprosy may also experience T1Rs (Kumar *et al.*, 2004). Older patients (≥ 15 years) may be at higher risk of T1R than children with leprosy (Ranque *et al.*, 2007). There is a strong link between facial patches and cutaneous T1R as well as between enlarged ulnar nerves and neural T1R (Roche *et al.*, 1997). Disease in more than two parts of the body increases the risk of developing T1R by a factor of ten (van Brakel & Khawas, 1994a).

A detectable bacterial load, which can be demonstrated by either a positive slit-skin smear, a positive PGL-1 or *M.leprae* DNA detectable by PCR, is a risk for T1R. A study in Nepal established that borderline patients with positive slit-skin smears were more likely to experience a T1R, and those who are seropositive for anti-PGL-1 antibodies have an a nine fold increased risk of T1R (Roche *et al.*, 1991). The presence of anti-PGL-1 antibodies in the serum has been shown to predict which patients are at greatest risk of NFI when used in conjunction with the WHO

classification in Bangladesh (Schuring *et al.*, 2008). Seronegative PB patients are at lowest risk of NFI with a cumulative incidence of 3.5%. Seropositive PB and seronegative MB patients have a medium risk of NFI of 13% and seropositive MB patients have a high cumulative risk of 53%. A study of 135 Brazilian patients with slit-skin smear negative single lesion paucibacillary leprosy showed that individuals with *M.leprae* DNA detectable by PCR in the skin were 2.5 times more likely to experience a T1R than those in whom *M.leprae* DNA was undetectable (Sousa *et al.*, 2007).

Nerve function impairment (NFI) present at leprosy diagnosis is a risk for reaction and further NFI. In the BAND Study in Bangladesh, 2510 PB and MB treatment-naïve patients were followed for three and five years respectively. 166 MB patients with NFI at diagnosis of leprosy developed new NFI; a 65% risk of NFI compared to the 16% risk in MB patients with no initial NFI. In the INFIR study (n=303), 188 participants did not have a T1R or NFI at baseline but had an abnormality in sensory nerve conduction in the ulnar and radial cutaneous nerves. Of them, 69 experienced a T1R and five experienced ENL during the two year follow-up period (Smith *et al.*, 2009). An abnormality in any nerve sensory conduction at the assessment immediately prior to the event was predictive. These data can be translated into the field where individuals, who have WHO disability grades 1 or 2 at diagnosis, are significantly more likely to have severe T1Rs (Schreuder, 1998a). Patients who have had one reaction episode are at higher risk of another episode; 31.8% had a recurrence in Hyderabad (Lockwood *et al.*, 1993).

Genetic regulation

A recent Canadian study identified a T1R genetic signature encompassing genes encoding pro- and anti-inflammatory mediators of innate immunity. In the T1R gene set, 29 genes were over-regulated and 15 genes were under-regulated. This suggests an innate defect in the regulation of the inflammatory response to *M.leprae* antigens and could be a future marker to identify patients at increased risk of T1R and nerve damage (Orlova *et al.*, 2013).

Pathology

Important diagnostic histological features of T1R are epithelioid cell granuloma oedema, dermal oedema, increase in number and size of giant cells and granuloma

fraction and epidermal expression of HLA-DR. Occasionally there is necrosis within the granuloma oedema. Intra-neural oedema was seen in biopsies from patients with new nerve damage in the INFIR study (Lockwood *et al.*, 2011).

Interestingly, the correlation between T1R diagnosed clinically and that diagnosed on biopsy is variable. One study in India showed that pathologists may under diagnose reactions in skin sections from patients with clinically apparent T1R by almost 50% (Lockwood *et al.*, 2008). A more recent publication discussed findings from the INFIR study cohort showing that clinicians were under-diagnosing reactions, as pathologists were possibly picking up sub-clinical reactions (Lockwood *et al.*, 2012b).

Immunology

T1Rs are the result of spontaneous enhancement of cellular immunity and delayed hypersensitivity reactions to *M.leprae* antigens presented by macrophages and dendritic cells in the skin and by Schwann cells on nerves (Lockwood *et al.*, 2002; Schenk *et al.*, 2012). *M.leprae* infection leads to the expression of major histocompatibility complex (MHC) II on the surface of the cells, and this gives rise to antigen presentation, which triggers CD4 lymphocyte-led killing of the cell by cytokines such as TNFα (Ochoa *et al.*, 2001). The increased rate of reactions in the first months after starting MDT may be explained by increased lysis of whole bacteria and release of antigen, which is then presented by immune cells.

During T1Rs, immunohistochemistry studies show increased levels of several Th-1 type pro-inflammatory cytokines, including IL-1, IL-2, IL-12, IFN-γ, iNOS and TNFα mainly locally (in skin lesions and nerves) but also systemically (in serum) (Khanolkar-Young *et al.*, 1995; Little *et al.*, 2001; Yamamura *et al.*, 1992). This results in oedema and painful inflammation in skin lesions and nerves. Interestingly, the levels of circulating cytokines do not reflect the local changes taking place in the skin during T1R. Treatment of the reaction causes clinical improvement, but changes in the inflammatory cytokines lags behind by some considerable time and in some may remain unchanged (Andersson *et al.*, 2005).

Clinical features

A T1R is characterised by acute inflammation in skin lesions and/or nerves. An Indian study found that the most common presentation of T1R was cutaneous lesions (74.41%) followed by cutaneous lesions and neuritis (53.6%), neuritis alone (12.1%), and finally only oedema of hands and feet (7.31%) (Sharma *et al.*, 2004). A small study in Nepal found that T1R affected skin only in 20%, skin and nerves in 50% and nerves only in 30% of patients (Walker *et al.*, 2011).

Skin lesions become acutely inflamed and oedematous (Figure 2.10). Erythema is often followed by desquamation (Figure 2.11) and sometimes ulceration. Inflammation is usually in pre-existing lesions, but not all the lesions may be involved. Lesions may be noticed by the patient for the first time because the inflammation makes the lesions obvious and painful. Oedema of the hands, feet and face can also be a feature of a reaction but systemic symptoms are unusual.

Nerves can become swollen, painful and tender. Acute neuritis (defined as spontaneous nerve pain, paraesthesia or tenderness with new sensory or motor impairment of recent onset) may also occur without evidence of skin inflammation. The inflammatory process in leprosy reactions leads to nerve function impairment (NFI) which if not treated rapidly leads to permanent loss of nerve function causing peripheral sensory and motor neuropathy.

Recurrent T1Rs can lead to further nerve damage (van Brakel & Khawas, 1994a). Progressive NFI can also occur in the absence of a reactional state, so the history of timing of symptoms aids to differentiate from NFI due to a reaction.

Figure 2.10 Clinical features of T1R

A 36 weeks pregnant woman with two week history of inflamed lesions on face. Note the oedematous, well-defined lesions as well as the oedema in the face, hands and legs.

Figure 2.11 Untreated T1R lesions

Desquamation in untreated T1R lesions of patient with BT leprosy, two months after acute inflammation.

2.2.2 Measuring severity of T1R

A tool which enables clinicians to accurately assess the severity of leprosy reactions is useful in determining outcomes for clinical trials. One of the earliest records of a severity scoring system for T1R was the "*indice névritique*", developed by Naafs and colleagues (Naafs & Dagne, 1977; Naafs & Droogenbroeck, 1977). This was a composite scale using various assessments of nerves including electrophysiological studies. It has not been validated. In a study of ulnar neuropathy complicating Type 1 and ENL reactions, another scale of severity was proposed. It was a composite of an assessment of spontaneous nerve pain with a visual analogue score, graded clinical assessment of nerve enlargement, monofilament sensory testing and voluntary muscle testing (Garbino *et al.*, 2008). This un-validated scoring system does not take into account T1R in skin lesions, and concentrates solely on neural signs.

In India, a scale devised as part of the INFIR Cohort study examined 21 items as the basis of a severity scale of both types of leprosy reactions and retrospectively assessed the performance of this scale (van Brakel *et al.*, 2007). There was good agreement between items in the scale. These included assessment of skin signs, fever, oedema and forms of neuritis plus changes in sensory and motor function assessed using monofilaments (200 mg, 2g, 4g, 10g and 300g) and voluntary muscle testing (VMT). As 298 patients assessed had T1R, whilst only five had ENL, so the focus of this scale was primarily on T1R, and reflected the importance of nerve function impairment in the severity grading of T1R. VMT and sensory monofilament testing had been previously shown to be reliable in the assessment of NFI (Anderson & Croft, 1999; van Brakel *et al.*, 2005b).

A 24-item scale based on the INFIR scoring system was used in two clinical trials: one study compared the effect of azathioprine and prednisolone in T1Rs (Marlowe *et al.*, 2004) and the second the effect of ciclosporin and prednisolone in T1Rs (Marlowe *et al.*, 2007). This scale was not validated.

A Severity Scale for T1R, based on the INFIR clinical severity scoring system, was developed and prospectively validated in Bangladesh and Brazil (Walker *et al.*, 2008). The first step involved gathering expert opinion on important clinical signs used to determine the severity of reaction. A score was then allocated to each of three sections. The first section looked at skin involvement using number of affected

lesions, the degree of inflammation and the presence of peripheral oedema. The second section was a measurement of sensory function of the nerves by using Semmes-Weinstein monofilaments to assess sensation in the hands and feet, and cotton wool for corneal sensation. In the third section motor function of the nerves of the face, hands and feet was assessed using the MRC grading. The overall severity scale score was the sum of the total for each section. The higher the score, the more severe the reaction. The scale was then validated by having each patient with T1R assessed by staff using the scale and then seen by an "expert" who would class the patient into mild, moderate or severe reaction. This was done independently and the results were correlated to assess agreement. Internal consistency of the scale was assessed and improved by removing three items: nerve pain, nerve tenderness and fever. Scale reliability was also assessed by having different observers performing the examination on the patients and correlating their results. This scale requires the examiner to be proficient in recognising the cutaneous signs of T1R, the assessment of muscle power by VMT and the use of SWM. It is mainly used in the context of research and referral settings. This Severity Scale for T1R has so far been used in clinical trials on intravenous methylprednisolone (Walker *et al.*, 2011), on azathioprine (Lockwood *et al.*, 2013) and in the on-going TENLEP studies (Wagenaar *et al.*, 2012).

2.2.3 ENL Reactions

Type 2 reactions are characterized by tender sub-cutaneous nodules, giving the condition the name Erythema Nodosum Leprosum (ENL). It is a humoral immunological response to *M.leprae* that commonly complicates lepromatous leprosy (LL) and less frequently borderline lepromatous (BL) leprosy. It usually affects multiple organs and causes systemic illness (Pfalzgraff & Ramu, 1994).

Epidemiology

A recent systematic review on epidemiological data of ENL found that accurate data on global and regional incidence is lacking (Voorend & Post, 2013). Six prospective and five retrospective studies gathered data from field programmes in which cumulative ENL incidence varied between 0.2% in an Indian study (Rao *et al.*, 1994)

and 4.6% in a Chinese study (Shen *et al.*, 2009). The incidence is reported as higher when ENL rate amongst MB patients only is recorded. Three prospective studies from the ALERT leprosy control services in Ethiopia reported cumulative incidence of ENL at 2.5% among MB cases after an average follow-up of two and a half years, but at 5% after ten years follow-up (de Rijk *et al.*, 1994; Becx-Bleumink & Berhe, 1992; Saunderson *et al.*, 2000a). In hospital settings ENL incidence in 28 studies ranged from 2% to 28.9% of MB cases (Voorend & Post, 2013). Published data suggest that there are regional differences in proportion of MB to PB cases, which may be reflected in the regional difference in ENL incidence.

Frequency of ENL according to the Ridley-Jopling classification has been reported in 16 small studies. In field studies, ENL in LL patients ranged between 11.1% and 26%, and in BL patients between 2.7% and 5.1%. Again higher proportions are found in hospital based studies. In Brazil, where ENL appears to be more frequent, one study reported 91% of LL patients developing ENL (Nery *et al.*, 1998). In a retrospective study of 481 BL and LL patients conducted in Hyderabad, ENL occurred in approximately 50% of LL and 9% of BL leprosy cases (Pocaterra *et al.*, 2006).

A high percentage of patients developing ENL do so during the first year of antimicrobial treatment (Feuth *et al.*, 2008; Pocaterra *et al.*, 2006), and can relapse intermittently over several years. Some authors suggest that since the introduction of MDT, the frequency and severity of ENL may have been decreased by the anti-inflammatory action of the clofazimine component of MDT (Pocaterra *et al.*, 2006; Balagon *et al.*, 2011).

Risk factors

A BI > 4 significantly increases the risk of developing ENL and degree of skin infiltration correlates positively with risk of ENL (Manandhar *et al.*, 1999). The odds ratio for developing ENL was 8.4 for individuals with LL and 5.2 for individuals with BL with a BI ≥ 4 (Pocaterra *et al.*, 2006). Similarly an Ethiopian study found ENL incidence was 9.6 times higher among LL patients compared to BL and BB (Becx-Bleumink & Berhe, 1992). In a Nepali retrospective study, it was found that fewer patients over 40 developed ENL and a higher ENL incidence was noted in patients diagnosed with leprosy in adolescence (Manandhar *et al.*, 1999).

Pregnancy and lactation appear to be significant precipitating factors for severe and recurrent ENL (Lockwood & Sinha, 1999). An Indian study implicated hormonal changes as 62% of the 32 women with ENL were either pregnant or lactating and 21% were menopausal (Arora *et al.*, 2008). An Ethiopian study among pregnant leprosy patients found an increased ENL incidence (22% among BL and 59% among LL) (Duncan & Pearson, 1984).

A recent Brazilian study found that patients with ENL were two times more likely to have an active co-infection than patients with T1R. Infections more commonly found in this group were chronic oral infections, urinary tract infections, viral hepatitis and intestinal parasites (Motta *et al.*, 2012). Although it has not been proven that other infections act as triggers to episodes of ENL, it is common practice to screen and treat patients presenting with ENL for co-infections.

Genetic expression

An American case-control study based in Nepal looked at 124 patients with ENL and found that four polymorphisms in the nucleotide-binding oligomerization domain containing 2 (NOD2) gene were associated with increased susceptibility to ENL in an allelic analysis, whereas seven out of 32 polymorphisms were associated with a dominant model (Berrington *et al.*, 2010).

Pathology

The histology of ENL skin lesions classically shows an intense perivascular infiltrate of neutrophils throughout the dermis and sub-cutis (Job, 1994). Polymorphs infiltrate the granuloma and there is vasculitis and macrophage degeneration together with breakdown of foam cells. Tissue oedema, vessels exhibiting fibrinoid necrosis and associated vasculitis may also be present. There is a local reduction in bacterial load; most of the organisms are fragmented and granular. During the healing phase neutrophils are replaced by lymphocytes. In a study of ENL lesions from Pakistani patients, 36% had no visible neutrophils and CRP was eight-fold lower in these patients (Hussain *et al.*, 1995). This study demonstrated that ENL lesions evolve rapidly and that the timing of biopsy samples is important for an accurate picture of the pathology (Mabalay *et al.*, 1965). Similar histological findings are found in nerves, muscle and lymph nodes when they are involved in ENL.

In the INFIR cohort, of 28 patients at risk of ENL, two were diagnosed clinically with ENL at entry whilst 13 patients had histological evidence of ENL on the skin biopsy at baseline. Only two out of the 13 patients with histological ENL went on to develop clinical ENL (Lockwood *et al.*, 2012b). It is important that both clinicians and pathologists be aware of local patterns of presentation and are able to detect changes in the patterns.

Immunology

ENL is due to a systemic inflammatory response to the deposition of extra-vascular immune complexes leading to neutrophil infiltration and activation of complement in many organs (Lockwood, 1996). It is associated with high levels of circulating tumour necrosis factor-α (Sarno *et al.*, 1991), interleukins IL-6, IL-10, IL-8, IL-12 (Moraes *et al.*, 1999) and IFNγ (Sreenivasan *et al.*, 1998), causing systemic toxicity. Circulating immune complexes are formed and deposited at sites distant from the bacilliferous lesions. This mechanism may account for the eruption of nodules in the skin at sites apparently previously unaffected and for the occurrence of nephritis, arthralgia and neuritis (Bryceson & Pfaltzgraff, 1990).

Direct immunofluorescence studies have demonstrated granular deposits of immunoglobulin and complement in the dermis in ENL lesions but not in those of uncomplicated LL disease (Wemambu *et al.*, 1969). There is evidence of T lymphocyte and macrophage activation and expression of mRNA for TNFα and IL12 in the skin (Moraes *et al.*, 1999). The ratio of CD4:CD8 cells is increased in ENL compared to uncomplicated LL (Kahawita & Lockwood, 2008) with a global decrease in CD8 numbers, suggesting that a cellular immune mechanism may in some way regulate expression of inflammation due to immune complexes. Despite increased cell immunity activity during ENL episodes, lepromatous patients revert to a state of immunological unresponsiveness after an episode of ENL.

Clinical features

The onset of ENL is acute, but it may pass into a chronic phase and can be recurrent. ENL produces fever, painful and tender skin lesions (Figure 2.12), uveitis, neuritis, arthritis, dactylitis (Figure 2.13), lymphadenitis and orchitis.

Figure 2.12 Acute ENL with multiple tender erythematous nodules

Figure 2.13 ENL dactylitis and bullous ENL, with ulcerated lesions

Figure 2.14 Chronic ENL lesions

Chronic ENL causes induration of skin with a repetitive cycle of new ENL nodules, ulceration and scarring; oedema is present.

The skin lesions of ENL are red papules or nodules that occur in crops often affecting the face and extensor surfaces of the limbs. Bullous ENL (Figure 2.13) has been described (Rijal *et al.*, 2004). Patients with chronic ENL show brawny indurations most frequently affecting the extensor surface of the thighs, calves and forearms (Figure 2.14). The recurrent inflammation of eyes can lead to blindness and of testes to sterility.

In a large retrospective study in India looking at reaction in a hospital setting, 25 patients with ENL were identified. ENL lesions presented chiefly as papulo-nodular lesions (92%) followed by pustulo-necrotic lesions (8%). Associated neuritis was found in 40% and peri-osteitis and iritis in 8% and 4% respectively (Sharma *et al.*, 2004). There is little data on the frequency and importance of the type of ENL lesions or the systemic features of ENL. A current multi-centred prospective study (ENLIST), looking at clinical features of ENL in 294 patients will shortly provide more detailed information (Walker *et al.*, 2012). Preliminary data from the 51 ENL patients recruited in the Ethiopian centre, ALERT, shows that 31% had ulcerating ENL nodules. Associated symptoms in this group were peripheral oedema (68%), neuritis (59%), bone pain (59%), muscle pain (55%) and orchitis (12%) (Doni & Lambert, 2013).

Three patterns of ENL were identified in a cohort of 82 Indian patients: single acute episodes, recurrent acute episodes and chronic ENL (Pocaterra *et al.*, 2006). Acute episodes were defined as single episodes responding to steroid treatment and accounted for only 6% of ENL cases, acute multiple ENL (32%) comprised of recurrent episodes with periods off treatment, and chronic when patients needed steroid treatment for more than six months (62%). A retrospective study of 563 Nepali patients with BL and LL leprosy found that 19% experienced ENL, and 45% of these had more than one episode of ENL (Manandhar *et al.*, 1999).

Episodes of active ENL have been reported to last from 14 days (Sehgal & Sharma, 1988) to 26.1 weeks (Balagon *et al.*, 2010). In Ethiopia, almost one third of patients developed a chronic condition lasting more than two years (Saunderson *et al.*, 2000a). ENL often has a protracted course with episodes occurring over seven or more years, although the majority last 12 to 24 months (Kumar *et al.*, 2004; Pocaterra *et al.*, 2006).

2.2.4 Measuring severity in ENL

No validated scales to measure severity of ENL have been published so far. A Cochrane review of treatments for ENL identified 13 clinical trials, of which only seven mentioned using an ENL grading system (van Veen *et al.*, 2009a). Each group of clinical researchers opted for a differing severity scoring system. Table 2.9 describes the grading system used in published retrospective studies, whilst Table 2.10 looks at those used in prospective studies.

In 1996 ILEP published definitions of mild and severe ENL which were updated in 2011(ILEP, 2011). Mild disease was defined as the presence of a few red nodules in the skin with low grade fever and malaise; treatable with analgesic or antipyretic drugs. Severe ENL included any or all of the following: neuritis with painful or tender nerves with or without loss of function; prolonged moderate or high fever with severe general malaise; pustular skin lesions which may progress to extensive ulceration; tender and enlarged lymph nodes; iridocyclitis, orchitis, periostitis or joint swelling; and albumin or red blood cells in the urine. Corticosteroid treatment with hospital admission whenever possible is advised for severe ENL. This system rated severity into mild and severe mainly on account of the number and characteristics of ENL skin lesions, automatically assuming high severity for most other accompanying systemic symptoms (including items such as severe malaise or prolonged fever). There is little clinical data to support this classification.

Authors	*Year*	*Study type*	*Details of grading system*
Becx-Bleumink and Berhe	1992	Retrospective, clinical course	ENL classified as severe if ulcerated nodules, or nerve function loss, +/-iridocyclitis, orchitis or dactylitis.
Pocaterra	2006	Retrospective, clinical course	Classified according to lesions and a global assessment score (anorexia, arthralgia, chills, malaise, neuritis, orchitis) on a 0-7 scale
Balagon	2011	Retrospective, clinical course	Mild ENL: less than 20 papulo-nodules without systemic signs and symptoms. Treatment with NSAIDs. Severe ENL: more than 20 papulo-nodules and/or constitutional symptoms, joint pains, edema, nerve involvement or ulceration. Severe ENL: > 20 weeks duration and total dose of prednisolone > 2gms
(Becx-Bleumink & Berhe, 1992; Pocaterra *et al.*, 2006; Balagon *et al.*, 2011)			

Table 2.9 Grading systems used for ENL severity in retrospective studies

Author & country	***Year***	***Study type***	***Patient number***	***Details of grading system***
Karat India	***1969***	Therapeutic. double blind	50	Graded 1-4 taking into account amount of nodules (few/ scattered/multiple), tenderness of nodules, nerve and bone tenderness, presence of oedema and systemic features as well as degree of oral temperature
Pearson Malaysia	***1969***	Therapeutic, double blind	12	Graded 0-4 scale for each component: severity of ENL (None/mild/moderate/requiring steroids - depending on "activity" of nodules); degree of temperature; elevation of WCC; stibophen and paracetamol requirement
Waters Malaysia	***1971***	Therapeutic, double-blind	10	Graded 0-5 looking at the distribution and type of lesions, level of malaise and degree of fever
Helmy Malaysia	***1972***	Therapeutic, double blind	15	Graded 0-4 following the scale by Pearson but with added details on the severity ENL lesions detailing activity of lesion varying from indolent to necrotic
Mathur India	***1983***	Therapeutic Case series	8	Classified as mild (nodules only), moderate (nodules with constitutional symptoms) or severe (if complications such as neuritis, bone pain and arthritis were present)
Arora India	***1985***	Therapeutic	12	Graded 0-4 with 0 denoting complete recovery from reaction; 1=nodules<15; little discomfort; 2= nodules 15-50 with moderate degree of constitutional symptoms and 3=severe with >50 nodules which may be ulcerative or necrotic with severe constitutional symptoms
Sampaio Nepal	***1998***	Prospective, double-blind	15	Graded I-III as follows: I – ENL nodules only II – ENL nodules + systemic symptoms III – EM-like lesions +/-systemic symptoms
Girdhar India	***2002***	Therapeutic	10	Graded 0-3 not clearly described but taking into consideration number, distribution and morphology of nodules as well as systemic features
Dawlah USA	***2002***	Therapeutic, double-blind	8	Recorded responses to treatment on 1-5 scale. 1=worsening of symptoms/signs after therapy 2= no effect 3-fair =some symptoms/signs resolved, most persist; 4-good= most symptoms/signs resolved, few persist; 5-excellent = complete resolution of signs/symptoms
Penna Brazil	***2005***	Therapeutic, double-blind	143	Number of skin lesions per body segment: mild was <10, moderate =10-20 nodules plus "some systemic symptomatology" and severe >20 nodules plus severe systemic involvement
Villahermosa Philippines	***2005***	Therapeutic, double-blind	22	Classified according to lesion count and a global assessment score (anorexia, arthralgia, chills, malaise, neuritis, orchitis) on a 0-3 scale (none, mild, moderate, severe)
(Karat *et al.*, 1969; Pearson & Vedagiri, 1969; Helmy *et al.*, 1972; Waters, 1971; Mathur *et al.*, 1983; Arora *et al.*, 1985; Sampaio *et al.*, 1998; Girdhar *et al.*, 2002; Dawlah *et al.*, 2002; Penna *et al.*, 2005; Villahermosa *et al.*, 2005)				

WCC=white cell count; ENL=erythema nodosum leprosum; LN=lymph nodes; EM=erythema multiforme.

Table 2.10 Grading systems used for ENL severity in prospective studies

The older grading systems used 40 years ago by Pearson (Pearson & Vedagiri, 1969), Helmy (Helmy *et al.*, 1972) and Waters (Waters, 1971) do not take into account the systemic features of ENL. Mathur's scale takes into account systemic features but not the severity of ENL nodules (Mathur *et al.*, 1983). The grading system suggested by Karat appears quite comprehensive as it takes into account the number and characteristics of ENL nodules, other symptoms and signs, oedema, features considered to be a sign of severity such as iritis, and temperature (Karat *et al.*, 1969). Arora, for the first time, suggested cut off points for the number of nodules, but "degree of constitutional symptoms" remained unclear (Arora *et al.*, 1985). Similarly, a more recent prospective study in Brazil comparing thalidomide regimen, graded ENL severity in 143 patients using a system based mainly upon the number of skin lesions present per body segment and the presence of systemic symptoms (Penna *et al.*, 2005). Mild ENL consisted of less than 10 ENL skin nodules per body segment, with mild pain and/or inflammatory symptoms and signs, and with no systemic symptoms. Moderate ENL consisted of 10 to 20 skin nodules per body segment and fever of moderate intensity (38-40˚C) with "some systemic symptomatology", including patients presenting with lymphadenopathy. Severe ENL described patients with more than 20 severely inflamed ENL lesions per body segment as well as severe systemic involvement. Again, the severity of 'systemic symptoms' is not clearly defined and it was presented as a subjective measure. The presence of lymphadenopathy automatically placed patients on a higher severity group although there is no evidence to support this. Their case definition for ENL left out all cases with neuritis and those with less than 10 skin lesions, meaning that the sickest and the mildest patients were excluded from the study.

In a randomized controlled study conducted in the Philippines of different doses of thalidomide, percentage of change in skin lesions was used as the outcome measure (Villahermosa *et al.*, 2005). This score was modified according to a semi-quantitative global assessment score that evaluated six key features (namely neuritis, arthralgia, orchitis, malaise, chills and anorexia) and graded 0-3 (0=none, 1=mild, 2=moderate, 3=severe) for severity. Although this scale is a composite measure of seven clinical features, it put greatest weight on ENL skin lesions, and the six key features of the global assessment missed out some key clinical features of ENL such as iritis and lymphadenopathy.

The grading system used in a retrospective study in India appears to be the most inclusive and reproducible system published to date and provides a specific classification system for severity that is based upon signs, symptoms and perceived response to treatment (Pocaterra *et al.*, 2006). It has the interesting attribute of incorporating responsiveness to treatment as one of the issues conditioning severity (Table 2.11). However, the items devised for the scale differ qualitatively and qualitatively at different severities, and the system does not provide a continuous score as such. As a result a patient cannot have varying amount of different disorders and instead, one "diagnosis" precludes others (i.e. despite all other symptoms, having iritis automatically places the patient in the severe group). This measuring system also highlights the lack of consensus that exists over the attributable severity of some clinical features in the context of ENL reactions. For instance, the presence of any neuritis or nerve function loss is deemed as severe according to most of the previous grading systems used for ENL severity, but considered as moderate here (Becx-Bleumink & Berhe, 1992).

Score	Description
0	No ENL
1	Very mild ENL – non-specific signs and symptoms, 1-2 non tender nodules, low/no fever, aches and pains
2	Mild ENL – few, tender skin nodules, low fever, malaise, few systemic symptoms
3	No ENL on steroids – absence during steroid intake
4	Mild ENL on steroid
5	Moderate ENL – mild + neuritis or more than 3 systemic symptoms
6	Severe ENL – toxicity, multiple nodules, high fever, dehydration, other organ involvement (orchitis, iritis, severe neuritis)
7	Intractable ENL – mild/moderate ENL while receiving steroids

Table 2.11 Pocaterra ENL severity grading system

With different grading systems, none of which have been validated, used in each study it makes any subsequent findings difficult to interpret and compare. Most of the studies were retrospective and the classifications were quite arbitrary with some authors including subjectively assessed components. Clinical data sets and the analysis of data from clinics is essential to support an accurate and replicable severity grading of ENL.

2.3 LITERATURE REVIEW OF REACTION TREATMENT

As both T1R and ENL are immunological processes, the treatment of these is based on immunosuppression. Corticosteroids have been used in the management of leprosy reactions for over 50 years but with limited initial data from clinical trials. Oral prednisolone is the most common treatment for severe reactions, but it is not always effective in leprosy reactions and alternative treatments are also discussed in this chapter.

2.3.1 Prednisolone

The use of adrenocorticotrophic hormone in the management of leprosy reactions was first reported by Roche et al in 1951 (Roche *et al.*, 1951). It is thought to act dually by reducing inflammatory oedema and inducing immuno-suppression. Steroids have a multitude of effects on both the metabolic and immune systems (

Table **2.12**) which cause some of the most serious adverse events.

Corticosteroids act via a genomic/nuclear–receptor mechanism by binding to specific glucocorticoid receptors (GR) in the cytoplasm of the cell. Once in the nucleus the GR-steroid complexes form dimers and bind to the promoter region of steroid responsive genes known as glucocorticoid response elements (GRE). Activation of GRE leads to the transcription of genes encoding anti-inflammatory mediators such as annexin-1, MAP kinase phosphatase-1, IκBα, secretory leukocyte protease inhibitor and glucocorticoid-induced leucine zipper (GILZ) (Barnes, 2006; Perretti & D'Acquisto, 2006). Activated GR-steroid complexes may also inhibit the activity of histone acetyltransferases (HATs), thus reducing the production of pro-inflammatory cytokines such as TNF- α, IL2 and IL6 (Ito *et al.*, 2000). The anti-inflammatory activities of steroids are both local and systemic.

Prednisolone is indicated in diseases with an anti-inflammatory or autoimmune component and it is used in an attempt to reduce features of inflammation and symptoms related to over activity of the host's immune response. Inflammation is controlled with prednisolone in rheumatoid arthritis (Clements & Davis, 1986), asthma (Kollef & Schuster, 1995), inflammatory bowel disease, Crohn's disease, and

ulcerative colitis (Faubion *et al.*, 2001) . Neurological indications for prednisolone are multiple sclerosis (Burton *et al.*, 2012), sub-acute demyelinating neuropathy (Kawanishi *et al.*, 2012), myasthenia gravis (Drachman, 1994) and Bell's palsy (Madhok *et al.*, 2009). Autoimmune conditions in which prednisolone therapy has been effective are autoimmune haemolytic anaemia (Lechner & Jäger, 2010), thrombocytopenic purpura (George *et al.*, 1994) and thyroiditis (Mizukoshi *et al.*, 2001). Topical preparations are effective in treating inflammatory conditions confined to the skin (psoriasis, urticarial reactions) or the eyes (episcleritis). Prednisolone is also used with other immunosuppressive agents to prevent graft rejection in organ transplantation (Appendix 2).

ANTI-INFLAMMATORY	Decreased adherence of neutrophils and macrophages at inflammation site Decreased proliferation and migration of lymphocytes and macrophages Decreased activation of plasminogen to plasmin Inhibition of phospholipase activity Decreased production of cellular mediators – cytokines, prostaglandins
METABOLIC	Increased glycogenesis and gluconeogenesis Increased protein catabolism and decreased protein synthesis Decreased osteoblast formation and activity Decreased calcium absorption from the gastrointestinal tract Decreased thyroid-stimulating hormone secretion

Table 2.12 Anti-inflammatory and metabolic actions of prednisolone
(Adapted from Shupnik – Human Pharmacology)

2.3.2 Prednisolone adverse effects

The First European Workshop on Glucocorticoid Therapy designated daily doses of prednisone between > 30mg and ≤ 100mg as "high doses" which are associated with severe side effects if used long term. This group also considers that side effects are considerable and dose dependent at "medium doses" of between > 7.5mg and ≤ 30mg (Buttgereit *et al.*, 2002). Steroid adverse effects are well documented (see Appendix 2) and are generally related to dose and duration of treatment. Their incidence increases steeply if dosage exceeds 7.5mg prednisone daily. Table 2.13 shows the known side effects of prednisolone.

Body system	Side Effect of Prednisolone
General	leucocytosis, hypersensitivity including anaphylaxis, thromboembolism, fatigue, malaise
Cardiovascular	congestive heart failure in susceptible patients, hypertension
Gastro-intestinal	dyspepsia, nausea, peptic ulceration with perforation and haemorrhage, abdominal distension, abdominal pain, increased appetite which may result in weight gain, diarrhoea, oesophageal ulceration, oesophageal candidiasis, acute pancreatitis
Musculoskeletal	proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, myalgia
Metabolic	sodium and water retention, hypokalaemic alkalosis, potassium loss, negative nitrogen and calcium balance
Skin	impaired healing, hirsutism, skin atrophy, bruising, striae, telangiectasia, acne, increased sweating, pruritis, rash, urticaria, may suppress reactions to skin tests
Endocrine	suppression of the hypothalamo-pituitary adrenal axis particularly in times of stress as in trauma surgery or illness, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, weight gain, impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, manifestation of latent diabetes mellitus, increased appetite
Psychiatric	euphoria, psychological dependence, depression, insomnia, dizziness, headache, vertigo, raised intracranial pressure with papilloedema in children, usually after treatment withdrawal. Aggravation of schizophrenia, epilepsy' suicidal ideation, mania, delusions, hallucinations, irritability anxiety, insomnia and cognitive dysfunction. In adults the frequency of severe psychiatric reactions has been estimated to be 5-6%
Ophthalmological	increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease
Immunosuppressive effects	increased susceptibility to and severity of infections with suppression of clinical symptoms and signs. Opportunistic infections, recurrence of dormant tuberculosis.
Withdrawal symptoms	too rapid a reduction of prednisone following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. A steroid withdrawal syndrome seemingly unrelated to adrenocortical insufficiency may also occur and include symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, weight loss, and/or hypotension.

Table 2.13 Known side-effects of prednisolone

(Summarized from prednisolone drug information sheet, Appendix 2)

One meta-analysis, including 6602 patients, reviewed the adverse effects of corticosteroid treatment compared to placebo treatment in double blind RCTs. The review found that minor dermatologic adverse effects (e.g. moon face, acne) and

diabetes, hypertension and psychosis were significantly more often reported in patients receiving steroids compared to patients in the placebo group. The occurrence of peptic ulcer did not differ significantly between the two groups (Conn & Poynard, 1994).

Doses of prednisolone greater than 20mg daily are immunosuppressive and may aggravate pre-existing infections and reactivate quiescent tuberculosis (Stuck *et al.*, 1989). Steroids may mask the symptoms of infection or cause the spread of infection in an unusual way making diagnosis more difficult (relative neutropenia) (Fekety, 1992). Diabetes and hyperglycaemia may occur during treatment with even low doses of corticosteroids (Gurwitz *et al.*, 1994). Long term prednisolone causes reduced bone metabolism resulting in osteoporosis and reduced secretion of growth factor from the anterior pituitary resulting in stunted growth in children (van Staa *et al.*, 2002). The behavioural effects associated with prednisolone therapy are due to its effect on the central nervous system. Although these initial effects are usually arousal and euphoria, prolonged treatment may cause depression, sleep disturbances and psychotic episodes (Sirois, 2003).

2.3.3 Prednisolone in Leprosy Reactions

Mode of action

Prednisolone reduces the production of pro-inflammatory cytokines. A study in 96 patients with T1R, median levels of IFN-γ and TNF-α fell during treatment with steroids; however TNF-α levels increased as the steroids were reduced. Median levels of IL-10 remained high throughout the steroid treatment period. Patients with high cytokine levels were found to have poor recovery of sensory and voluntary muscle nerve function, higher risk of reactivation of T1R symptoms during steroid treatment and higher risk of another episode of T1R within a few months of completing steroid treatment (Manandhar *et al.*, 2002). The need for prolonged treatment with steroids is supported by studies showing that Th1 cytokine (IFN-γ, IL-12) activity continues even 180 days after the start of prednisolone in T1R in three out of five patients tested (Little *et al.*, 2001). Steroids also act by inhibiting the enzyme prostaglandin synthetase and decreasing chemotaxis of neutrophils. The

associated suppression of CMI and decreased release of pro-inflammatory lymphokines makes prednisolone a useful drug for managing ENL.

Effectiveness of prednisolone in T1R

The 8th Report by the WHO Expert Committee on Leprosy (WHO, 2012b) states that "severe reversal reactions should be treated with a course of steroids, usually lasting 3-6 months". The standard regimen for treating T1R or neuritis in most countries is prednisolone 40mg daily, with the dose decreasing 5mg every 2-4 weeks after evidence of improvement, and usually given for 12 to 20 weeks in total. In severe T1R, the starting dose of prednisolone may be 60mg and above. However, several studies have shown that a significant number of patients show no improvement in nerve function impairment (NFI) and have multiple episodes of T1R.

The treatment of T1Rs is aimed at controlling the acute inflammation in skin and nerves, easing pain and reversing nerve damage. There are few good data for making evidence-based treatment decisions about managing T1Rs or NFI. This was highlighted by the Cochrane systematic review "Corticosteroids for treating nerve damage in leprosy" (van Veen *et al.*, 2007), where only three randomized controlled trials could be included in the review. The sole trial which examined the effect of corticosteroids in T1R did not fulfil the initial inclusion criteria of the review. The systematic review concluded that evidence for the efficacy of corticosteroids is lacking, and that the optimal dose and duration of treatment is unclear; there is a need for larger, well controlled randomised studies.

The main difficulty with interpreting the data and assessing the impact of steroid treatment from these studies is due to the difference in entry criteria, outcome measures and study methodologies. Some studies looked at T1Rs and ENL together despite their different aetiology, clinical presentation and response to treatment. It is difficult to compare studies that use "improvement" as an outcome with those that use the more stringent criterion of recovery. In many studies different features of nerve involvement such as nerve function impairment and neuritis were used, as entry criteria and outcome measures. Not differentiating between old and new NFI at entry level complicates the interpretation of treatment efficacy further.

Published studies on the effect of corticosteroids are summarized in Table 2.14 to Table 2.16. Retrospective studies on the effect of corticosteroids on T1Rs and/or NFI in patient series from Ethiopia, India, Nepal and Indonesia indicate that corticosteroids are not entirely effective in the treatment of T1Rs or isolated nerve function impairment (Table 2.14). Both retrospective and prospective cohorts, only six of which are randomized studies, suggest a large percentage of patients with NFI/T1R do not respond to corticosteroids (Table 2.15 and Table 2.16).

The Ethiopian AMFES study, a prospective cohort study following 594 MB leprosy patients after MDT treatment found that a six month course of prednisolone resulted in no improvement in 27% of patients. It also reported that 50% of patients with acute NFI (i.e. less than six months duration prior to start of treatment) would recover nerve function if steroids were used for a median time of 6.5 months, but the maximum time to nerve recovery could be as long as 45 months (Saunderson *et al.*, 2000d). The evidence for poor treatment response in NFI older than six months comes from TRIPOD 3, a double-blind placebo-controlled trial of patients with untreated NFI between 6 and 24 months duration. Subjects were randomised to either prednisolone treatment or placebo. No additional improvement in long standing NFI, or prevention of leprosy reactions was seen in the patients treated with prednisolone (Richardus *et al.*, 2003b).

A Bangladeshi study showed that in a group of 132 patients with acute NFI, 32% of impaired nerves did not respond to prednisolone and that 12% of impaired nerves had functional deterioration despite treatment (Croft *et al.*, 2000). In Hyderabad, only 50% of patients with reactions attending out-patients clinic showed improvement in nerve function after six months of steroid treatment and almost 32% had repeated episodes of T1R (Lockwood *et al.*, 1993).

Retrospective reports of studies in T1R or NFI					
Country, Author, Year and Type of study	**Criteria for review**	**Number analysed**	**Outcome Measures**	**Conclusion by authors**	**Conclusion by Saba Lambert**
India (Santaram & Porichha, 2004)	**All reactions**	**101 Type 1 reactions of 942 cases**	**"Satisfactory response"**	**95.2% of all reactions had satisfactory response**	**Outcome not measurable**
Indonesia (Bernink & Voskens, 1997) **Field study**	**Nerve function impairment in all types of reaction**	**154**	**Improvement, the same or worse after 10 weeks of pred-nisolone starting at 40mg, reducing**	**75-80% of affected nerves improved either partially or totally**	**20-25% of nerves did not improve at all**
Nepal (van Brakel & Khawas, 1996)	**Nerve function impairment**	**168**	**Comparison of nerve function at 3 and 6 months after steroids starting at 40-60mg reducing over 12 weeks**	**Nerve function improved in 30-84%**	**Up to 47% showed no functional improvement**
India (Lockwood *et al.*, 1993) **All cases from 1985**	**Type 1 reaction**	**44 Type 1 reaction of 494 cases**	**Improvement in symptoms and signs**	**93% of skin lesions and 50% of neuritic episodes responded.**	**50% of NFI did not improve** **31.8% had repeated episodes of T1R**
Ethiopia (Becx-Bleumink & Berhe, 1992) **Field study**	**All reactions**	**142 Type 1 reactions**	**Recurrent reaction Nerve function loss**	**88.2% regained complete or partial recovery of the nerve function**	**11.8% of patients showed no improvement.** **30% of BL patients had recurrence of RR where steroids stopped.**
India (Kiran *et al.*, 1991)	**≤6 months of facial nerve damage with lagophthalmos**	**27 patients (36 eyes)**	**Degree of eyelid lag in mm (12 week regimen starting at 30 or 40mg)**	**75% had improved facial nerve function (complete eye closure or less than 2mm lag)**	**25% showed no improvement**
Ethiopia (Naafs *et al.*, 1979)	**Neuritis in selected patients**	**48**	**VMT deficit**	**A longer course (6-9 months) is better than a short one (1-2 months).**	**Only VMT as outcome, unclear measure**

Table 2.14 Retrospective studies using prednisolone in T1R
(Tables are adapted from Stephen Walker 2009)

Prospective randomised studies of prednisolone in T1R or NFI						
Country, Author Year and Type of study	**Entry criteria**	**No. Enrol-led**	**Intervention**	**Outcome measures**	**Conclusion by authors**	**Conclusion by Saba Lambert**
Nepal (Walker *et al.*, 2011) **Double blind randomised controlled**	**T1R and/ or NFI alone of less than 6 months duration**	**42**	**Methylprednisolone 1g i.v. for 3 days followed by pred 40mg daily reducing over 109 days to 0 versus pred 40mg daily reducing over 112 days.**	**Change in Clinical Severity Score and NFI Time to next steroid requiring episode. Amount of extra pred required**	**No significant difference between the two groups**	**Nearly 50% of individuals required additional prednisolone.**
Brazil (Garbino *et al.*, 2008) **Randomised controlled**	**Ulnar neuropa-thy associated with T1R or ENL**	**21 (27 nerves)**	**Prednisone 2mg/kg/day initially compared with 1mg/kg/day initially for controls. Tapered variably.**	**Clinical Score and motor nerve conduction**	**Higher initial dose showed better improve-ment initially. Early initiation of treatment is most important factor for better recovery**	**Unclear rate of recovery**
India (Rao *et al.*, 2006) **Double-blind randomised controlled, parallel group**	**"Severe" Type 1 reactions**	**334**	**3 prednisolone regimes: 3.5g over 5 months 2.31g over 5 months 2.94g over 3 months**	**Amount of extra prednisolone required (for either skin and/or nerve reaction)**	**Patients requiring extra pred was: 46% in 3/12 group 31% in 5/12 low dose group 24% in 3/12 high dose group**	**Extra prednisolone is required by 24% even in the longer and higher dose regimens of prednisolone**
Nepal (Marlowe *et al.*, 2004) **INFIR 2 Randomised controlled**	**Type 1 reactions skin or skin and nerve**	**40**	**12 weeks azathioprine and 8 weeks prednisolone compared to 12 weeks prednisolone alone**	**Clinical Severity Score: Skin signs, nerve tenderness, and NFI Amount of extra pred required**	**Regimens equally effective 52-63% skin signs improved 50-63% ST and VMT improved**	**More than 37% of nerves and skin signs did not improve on either Rx Relapse in skin signs 30%**
Nepal, Bangladesh (Richardus *et al.*, 2003b) **TRIPOD 3 Double blind RCT, placebo controlled**	**NFI of 6-24 months duration.**	**92**	**16 week standard prednisolone regime**	**Sensory and motor test scores**	**No difference in improvement between prednisolone (57%) and placebo group (59%)**	**No benefit in treating NFI greater than 6 months duration**
Nepal, Bangladesh (van Brakel *et al.*, 2003) **TRIPOD 2 Double blind RCT, placebo controlled**	**Isolated mild sensory impairment, less than 6 months duration**	**75**	**16 week standard prednisolone regime**	**Improvement in monofilament scores.**	**No difference in improvement of ST between treated (80%) and untreated groups (79%).**	**20% of patients with mild ST did not improve, but deteriorated**

Table 2.15 Prospective randomised studies with prednisolone in T1R or NFI

Non-randomised prospective studies of prednisolone in T1R or NFI						
Country, Author, Year and Type of study	**Entry criteria**	**No.**	**Intervention**	**Outcome measures**	**Conclusion by authors**	**Conclusion by Saba Lambert**
Ethiopia (Saunderson et al. 2000b) AMFES Prospective observation field study	Neuropathy including nerve tenderness	594	Steroid regimes for PB (12 weeks) and MB (24 weeks) patients	Motor and sensory testing and symptom improve-ment	88% of patients with acute NFI recovered fully, and 51% of patients with chronic/ recurrent NFI recovered	27% of patients did not improve, and 59% had recurrent episodes of NFI
Bangladesh (Croft et al. 2000) Prospective, open, uncontrolled	NFI	132	16 week standard prednisolone regime	Improve-ment	68% of sensory nerves and 67% of motor nerves showed improvement at 12 months,	A core of 32% of impaired nerves did not respond to prednisolone, and 12% of impaired nerves had functional deterioration despite treatment
Thailand (Schreuder, 1998b) Observation study	Newly diagnosed leprosy patients	640	Not clear	Nerve function	Nerve damage at presentation improves in only 44% compared to 82% improvement in damage developing whilst on treatment	18% of new NFI and 66% of old NFI did not improve
Nepal (Wilder-Smith & Wilder-Smith, 1997)	Autonomic nerve dysfunction Motor and sensory deficit	18	Prednisolone starting at 40mg and tapered according to individual response	Nerve function	Improvement in vasomotor function (14.8%), Sympathetic skin response (16.6%) sensory function (21.2%) and motor function (1.3%)	About 80% of small nerve damage does not improve
India (Kiran *et al.*, 1985) ? Prospective Open.	Impaired VMT or ST	33	Semi-standardized prednisolone regime	Nerve score	Good result in 74% of nerves (No controls)	Outcome difficult to assess
Ethiopia (Touw-Langendijk *et al.*, 1984) Open uncontrolled	Recent nerve function loss	36	6 month course of prednisolone	Sensory and motor function	63% of affected nerves (59/93) "improved"	37% of nerves did not improve

Table 2.16 Non-randomised prospective studies of prednisolone in T1R or NFI

Several studies have indicated that some NFI will improve without steroid therapy. This improvement may be spontaneous or attributable to MDT (Croft *et al.*, 2000; Saunderson *et al.*, 2000d; Schreuder, 1998b). The BANDS cohort included 69 individuals with NFI who should have received prednisolone but did not. In these patients 33% of involved motor nerves and 62% of sensory nerves had some degree of improvement at 12 months follow-up (Croft *et al.*, 2000). The AMFES cohort included 141 individuals with NFI at the time of enrolment which had been present for longer than six months and so were not treated with steroids. Between 25% and 33% of nerves with this longstanding impairment improved fully during the long period of follow-up (Saunderson *et al.*, 2000d). The phenomenon of spontaneous improvement in nerve function is another confounder in determining the size of the effect of any intervention being studied.

Despite different regimes of oral prednisolone having been employed in the management of individuals with inflamed skin plaques, neuritis or NFI, optimal dose and duration of prednisolone treatment have not been established yet. A randomized study of three different prednisolone regimes suggested that duration of treatment, rather than the starting dose of prednisolone, may be more important in controlling T1Rs (Rao *et al.*, 2006). In this Indian multi-centre study, 334 patients, both with and without nerve involvement, were treated with prednisolone. The primary outcome measures were failure to respond to treatment and physician determined requirement for additional prednisolone rather than improvement in nerve function or skin signs. Initial prednisolone 30mg tapered slowly to zero over 20 weeks (total dose=2.31g) was a superior regimen to initial prednisolone 60mg tapered over 12 weeks (total dose= 2.94g). There was no significant difference between the two prednisolone regimens with differing initial doses of 30mg or 60mg (total dose=3.5g) but both tapered over 20 weeks. Although the outcomes were poor criteria and not easily reproducible without bias, only 24% of patients in the five month course needed extra prednisolone compared to 46% in the three month course.

There are also no good data on the optimum initial dose of steroid. The trial from Brazil (Garbino *et al.*, 2008) showed that in patients with ulnar nerve neuropathy, those on higher doses of prednisolone had better results initially but no significant differences were seen at later reviews between the two dosage regimen (2mg/kg/day versus 1mg/kg/day). The trial by Walker showed that a three day course of

methylprednisolone at the start of treatment does not improve outcomes and that nearly 50% of the 42 patients needed extra prednisolone to control deterioration of nerve function or a recurrence of T1R (Walker *et al.*, 2011).

TRIPOD 1 (Trials in Prevention and Disability) conducted in Nepal and Bangladesh, tested whether addition of low dose prednisolone to MDT can prevent reaction and NFI (Smith *et al.*, 2004). Patients with new MB leprosy (636) were randomised to MDT plus prednisolone 20mg/day for three months, with tapering dose in the 4th month, or to MDT plus placebo. The use of low dose prophylactic prednisolone during the first four months of multi-drug treatment for leprosy reduced the incidence of new reactions and nerve function impairment in the short term, but the effect was not sustained at one year. The preventative effect of prednisolone at four months was more than three times higher in patients with no pre-existing NFI. In low-income settings, where infections such as TB predominate, the risks of giving long-term prophylactic prednisolone, with all the known side effects, outweighs the benefit.

Studies are underway to assess the treatment of early neuropathy (TENLEP): one to determine whether prednisolone treatment of early sub-clinical NFI can prevent clinical NFI, and the other to assess whether prednisolone treatment of 32 weeks duration is more effective than 20 weeks (Wagenaar *et al.*, 2012).

In summary, from the available published data we can conclude that prednisolone is effective in treating between 60-70% of NFI and T1R. The more stringent the outcome measures of the studies, the higher the percentage of NFI that does not improve or recover (30-40%) with steroid treatment. New NFI (less than six months duration) has better rates of recovery than old NFI, and that courses of prednisolone of 20 weeks or longer are better than 12 weeks courses. Recurrence of NFI and T1R are common, occurring in 30-50% of patients, and extra prednisolone is often needed to control signs of T1R. These longer courses of prednisolone put patients at higher risk of adverse events.

Alternatives to prednisolone in T1R

Non responsiveness or "resistance" to corticosteroid therapy has been described in a proportion of individuals with inflammatory conditions such as asthma, rheumatoid

arthritis (RA) and inflammatory bowel disease (Barnes & Adcock, 2009a). The molecular mechanisms that have been postulated to underlie this include reduced corticosteroid-corticosteroid receptor binding, defective nuclear translocation and reduced histone acetylation. It is not known how common the phenomenon of corticosteroid resistance due to such physiological factors is in patients with leprosy reactions, but it has been demonstrated from the studies above that prednisolone is not 100% effective in the management of leprosy T1R and NFI.

The assessment of alternatives to prednisolone is needed in several different contexts. Firstly, the value of other immune-suppressants themselves needs to be assessed. Are there more efficient agents than prednisolone for the treatment of reactions? Secondly, there are currently little data on the utility of potential drugs as second line treatments. There are currently few therapeutic alternatives for patients who do not respond to prednisolone (about 40%) or who cannot take prednisolone because of adverse effects.

Methotrexate has good anti-inflammatory properties but there is only one report in which it was used successfully in T1R to reduce steroid dose in a patient with borderline leprosy intolerant to steroids (Biosca *et al.*, 2007).

Azathioprine in combination with an eight week course of prednisolone was as effective as a 12 week course of prednisolone in the management of T1Rs in a pilot study in Nepal (Marlowe *et al.*, 2004). This randomized controlled study with 40 patients showed that azathioprine was well tolerated but further studies were needed to assess its uses as a steroid-sparing drug.

Mycophenolate mofetil affects both B and T lymphocyte activity resulting in immunosuppression and was theoretically expected to work on both types of reaction. However it was found not to be useful in any type of reaction (Burdick & Ramirez, 2005). Similarly, no significant results were seen with the use of pentoxifylline in T1R (Dawlah *et al.*, 2002).

Ciclosporin has been used in pilot studies in Nepal and Ethiopia with some success (Marlowe *et al.*, 2007). This is discussed in detail in the Chapter 2.5.6.

Effectiveness of prednisolone in ENL

Steroids have been the main treatment for ENL since the 1950's. A Cochrane review found that the few studies on the management of ENL (van Veen *et al.*, 2009a) were small and poorly reported and that no clear benefit for interventions could be found from the 13 RCTs selected. Table 2.17 describes the RCTs in which prednisolone was tested against another agent in the management of ENL.

Country, Author Year and Type of study	Entry criteria	No. Enrol-led	Intervention	Outcome measures	Conclusion
Singapore (Ing, 1969) Randomised, blind, parallel	LL and ENL (mild, moderate & severe)	30	1 month of prednisolone (5mg 3 times a day) vs. 1 month of indomethacin 25mg 3 times a day	Subsidence of lesions and pain relief	No significant difference
India (Karat *et al.*, 1969) Randomised, blind, parallel	LL and ENL	50	4 groups: indomethacin, chloroquine, prednisolone (5mg three times a day) and aspirin	Control of reaction, recurrence at 90 days and at 12 months	No significant difference
India (Karat *et al.*, 1970) Randomised, parallel	Severe recurrent ENL (more than 3 ENL episodes)	24	2 groups: clofazimine 100mg 3 times a day for 12 weeks vs. prednisolone (10mg three times a day) gradually decreasing over 12 weeks	Treatment success at 12 weeks: normal temp, no new ENL lesions, no neuritis, no iritis Recurrence of reaction	More treatment success (RR 3.67; 95%CI 1.36 to 9.91) with clofazimine; but no difference in recurrence at 12 weeks
India (Girdhar *et al.*, 2002) Randomised, parallel	LL with recurrent ENL	10	Betamethasone iv 3 days a month for 6 months vs. 5% dextrose	Change in severity and frequency of ENL Steroid requirement	No significant difference

Table 2.17 Prospective randomised studies using steroids in ENL

Looking at the evidence from these studies, it would appear that prednisolone in the management of ENL is of no advantage compared to indomethacin, aspirin, chloroquine, clofazimine or even dextrose. It could be that the doses of prednisolone used in these studies were too low. As severe ENL is a debilitating multi-system condition, the use of a potent immunosuppressant is essential.

The ILEP Technical Bulletin on the management of ENL recommends treating severe ENL with corticosteroids at a starting dose of 30-60mg and reducing every week by 5-10mg. A maintenance dose of 5-10mg may be needed for several weeks

to prevent recurrence of ENL (ILEP, 2011). The WHO 8th Expert Committee on Leprosy report recommends that severe ENL should be treated with a 12-week course of prednisolone (daily dosage not exceeding 1mg/kg body weight) (WHO, 2012b). This overlooks the chronic and recurrent nature of ENL and is not supported by any data.

Individual ENL episodes are generally thought to be short lasting. The therapy with higher dose of steroids should theoretically be confined to the acute period of ENL which generally resolves rapidly. Theoretically a short course of prednisolone would be sufficient, but ENL has a high recurrence rate. Prednisolone does not prevent recurrences and usually an ENL flare-up occurs when prednisolone doses are decreased to 20-30mg per day (Garbino *et al.*, 2008). Clinical experience suggests that, with time prednisolone resistance develops, leading to higher doses of prednisolone being needed to control ENL flare-ups. This is further complicated by the occurrence of NFI in ENL. NFI in patients with ENL may be under-treated if the short ENL regimes are followed. Longer periods of steroid treatment for NFI have been shown to be more effective (Rao *et al.*, 2006). The repetitive character of ENL neural involvement could be a major factor influencing the poor results of long term treatment of ENL.

Many of the outcome measures in the clinical trial discussed in the Cochrane review on ENL management, are easily measured and replicable (van Veen *et al.*, 2009a): percentage achieving remission in skin lesion secondary to ENL or remission of inflammation at other sites; time to next clinical episode of ENL; frequency in ENL episodes; amount of extra prednisolone needed and rate of adverse events. Other outcomes such as investigator assessed change in ENL severity or change in quality of life are very subjective unless validated tools are used to measure this.

With ENL being a mostly chronic debilitating multi-system condition, an efficient treatment is essential. High dose prednisolone is efficient in controlling the signs and symptoms of ENL within a few days, but it is not efficient in preventing the frequent flare-up. The frequent long courses of prednisolone needed to control ENL in patients result in multiple adverse events. Alternative, more efficient treatments are essential.

Alternatives to Prednisolone in ENL

Treatment of ENL remains challenging. The 13 randomised controlled trials (445 participants) for ENL, assessed in Cochrane Review, were of poor quality (van Veen *et al.*, 2009a). Interventions assessed were: bethamethasone, thalidomide, pentoxyfylline, clofazimine, levamisole and indomethacin. No significant benefit was found in the following studies: pentoxifylline compared to thalidomide (1 trial, 44 participants) (Sales *et al.*, 2007), aspirin or chloroquine treatments (2 trials, 80 participants) (Karat *et al.*, 1969), or levamisole compared to placebo (1 trial, 12 participants) (Arora *et al.*, 1985). Colchicine has also been used for mild to moderate ENL with limited effect (Sarojini & Mshana, 1983; Sharma *et al.*, 1986).

Clofazimine has mild anti-inflammatory activities which are useful in the management of ENL (Helmy *et al.*, 1972). Its mechanism of action is not clearly understood and it is slow to act. In randomized controlled trials clofazimine treatment was associated with a significant benefit in terms of severity reduction compared to placebo (Helmy *et al.*, 1972), more treatment success compared to prednisolone: RR 3.67; 95% CI 1.36 to 9.91 (1 trial, 24 participants) (Karat *et al.*, 1970) and fewer recurrences compared to thalidomide: RR0.08; 95%CI 0.01 to 0.56) (1 trial, 72 participants) (Iyer & Ramu, 1976). It is thought that the daily dose of 50mg in MB MDT probably controls the severity and frequency of ENL in at risk individuals (Cellona *et al.*, 1990). This protective effect is lost once the course of MDT finishes. In the management of ENL, clofazimine is used in larger doses than those in MDT, starting at 300mg a day (Schreuder & Naafs, 2003). It does not relieve acute manifestations of ENL, but given over several weeks it may both reduce the severity of ENL flare-up and the dose of steroids needed to control recurrent ENL (Balagon *et al.*, 2011). Disadvantages of continuous high doses of clofazimine are gastrointestinal symptoms (cramping, diarrhoea, bowel obstruction) and skin discolouration (Jopling, 1976; Mason *et al.*, 1977). The dose of clofazimine is gradually decreased after the first 12 weeks, with a total maximum treatment period of 12 months (WHO, 2012b).

In 1965, Sheskin reported the effectiveness of thalidomide in the management of ENL (Sheskin, 1965). It is a potent suppressor of TNF release (Sampaio *et al.*, 1993) as well as a sedative. Thalidomide (300 to 400mg daily) has a dramatic effect in controlling ENL and preventing recurrences (Moreira *et al.*, 1998). It is able to

suppress all clinical manifestations of ENL within 48 to 72 hours. Its action is faster and more effective than aspirin (Iyer *et al.*, 1971), clofazimine (Iyer & Ramu, 1976) and pentoxyphilline (Sales *et al.*, 2007). Four RCTs showed that treatment with thalidomide had a significant benefit compared to placebo although significance disappeared when studies were pooled (van Veen *et al.*, 2009a).

Thalidomide is used as first line treatment for ENL in Brazil and a few other countries. But its use is limited by teratogenicity and possible neuropathy (Walker *et al.*, 2007). It is also not available in many countries and the cost can be prohibitive. In some settings thalidomide is given under strict precautions to men only, others may include post-menopausal women or only hospitalised patients.

Two cases of patients with ENL have been reported in whom TNFα blockade with the biological drug infliximab was used successfully (Faber *et al.*, 2006; Ramien *et al.*, 2011). In leprosy endemic settings, the risk of TB and other difficult to diagnose infections may be a contraindication to the use of these drugs. The current cost of these agents will also limit their use.

Following the first case report on the use of methotrexate in the management of ENL (Kar & Babu, 2004), a case series of nine patients with severe recurrent ENL reported possible successful treatment with a combination of methotrexate and prednisolone (Hossain, 2013). There has also been a case report on the successful use of azathioprine in one patient with ENL (Verma *et al.*, 2006). Further studies are needed to assess these two drugs.

Effective ciclosporin use has been reported in a few cases of ENL. This is discussed in detail in chapter 2.5.6.

Adverse effects of prednisolone in reactions

Complications of long-term steroid therapy are well known and have been reported in leprosy studies. There are little data on adverse events collected systemically in prospective leprosy reaction trials. Analysis of the adverse events attributable to prednisolone in the three TRIPOD trials suggests that the drug is safe when used under field conditions in standardised regimens (Richardus *et al.*, 2003a). The trials used total prednisolone doses of 1.96g and 2.52g. They found that the relative risk of developing minor adverse events was higher in patients treated with prophylactic

prednisolone regimen (RR=1.6). These minor events were acne, moon face, cutaneous (including nails) fungal infections and gastric pain requiring antacids. There was no difference in the likelihood of major adverse events between the prednisolone and placebo groups. However, the dose and duration of prednisolone used to treat patients with T1R or ENL are usually higher than those in the TRIPOD studies. A standard six months course of prednisolone for T1R in Ethiopia would have a cumulative dose of 3.9g, which becomes much higher if there are recurrences of T1R. The TRIPOD studies also defined a set of major events related to prednisolone. These included peptic ulcer, diabetes mellitus, psychosis or other mental health problems, glaucoma, cataract, hypertension, infections, infected ulcers, corneal ulcer and tuberculosis.

In patients with leprosy reactions, there are few data concerning the long term sequelae of corticosteroids use. In a large, retrospective series of 581 Indian patients with T1R, 2.2% developed diabetes requiring an oral hypoglycaemic agent during the initial phase of treatment with corticosteroids (Sugumaran, 1998). Cataract formation is a recognised complication of corticosteroid therapy but may also complicate leprosy (particularly smear positive disease) per se (Daniel & Sundar Rao, 2007). Cataract was identified in 4% of individuals treated for T1R in the Indian study above, but all of these patients had been on steroids for more than 12 months (Sugumaran, 1998). There are no studies on the extent of bone demineralization in leprosy patients treated with steroids or interventions that might improve or prevent it. There are some reports of osteoporotic fractures in leprosy patients on prednisolone (Alembo *et al.*, 2013; Garbino *et al.*, 2008).

Lately, adverse events are being reported more accurately in leprosy RCTs. In the study of prednisolone versus methylprednisolone and prednisolone, 23 patients out of 40 experience at least one steroid related side effect. Moon face, acne and gastric pain were the most common whilst two major adverse events were recorded: one patient developed glaucoma and one patient an infected neuropathic ulcer (Walker *et al.*, 2011).

We recently conducted a review of all patients in reaction admitted to ALERT hospital in Ethiopia during a five year period. Of the 309 patients, 99 had ENL and 145 had T1R. Eight patients with ENL died compared with two diagnosed with T1R. This difference is statistically significant (p=0.0168, Fisher's Exact Test). All the

deaths in the ENL group were attributable at least in part to corticosteroids and all the deaths occurred in individuals who had been taking corticosteroids for a continuous period of at least 18 months. Two deaths were possibly due to ENL itself. There was considerable morbidity associated with corticosteroid therapy in the ENL group including osteoporosis, hypertension, diabetes mellitus, strongyloidiasis and tuberculosis (Walker *et al.*, 2014).

2.3.4 Ciclosporin

Ciclosporin (also known as Ciclosporine and Cyclosporine A) was first investigated as an antifungal in 1972, by Sandoz (now Novartis) in Basel, Switzerland. Although it was found to have only a mild bacterio-static effect, it had a potent immunosuppressant effect. In 1980 it was used for the first time on a human patient to prevent organ rejection after a liver transplant. It was approved for use in 1983.

In inflammatory conditions an antigenic signal from antigen-presenting cells (APC) stimulates T cells via the T cell receptor and this causes activation of calcineurin (Figure 2.15). Activated calcineurin allows dephosphorylation of nuclear factor of activated T cell (NFAT), enabling NFAT to enter the T cell nucleus and bind to the IL-2 gene promotor region. This results in increased production of IL-2, which in turn allows T cells to enter the cell cycle and proliferate. Ciclosporin inhibits this process by binding to the T cell cytoplasmic receptor, cyclophylin. The Ciclosporin/cyclophylin complex then inhibits the activation of calcineurin and therefore IL-2 production and T cell proliferation. Ciclosporin is thought to selectively inhibit CD4 T cells, not CD8 T cells, thereby also associated with reduction in expression of cytokines produced by CD4 cells: IL-2, IFN-γ, IL-3 and TNFα (Hess *et al.*, 1982; Di Padova, 1990; Stein *et al.*, 1999). A more recent study in Brazil found that in the treatment of chronic neuritis with ciclosporin, anti-nerve growth factor antibody levels were lowered to levels similar to those in normal subjects (Sena *et al.*, 2006).

The main site of ciclosporin absorption is the upper intestine. It has a narrow therapeutic window, which means that too low a dose is ineffective and too high a dose may lead to adverse events.

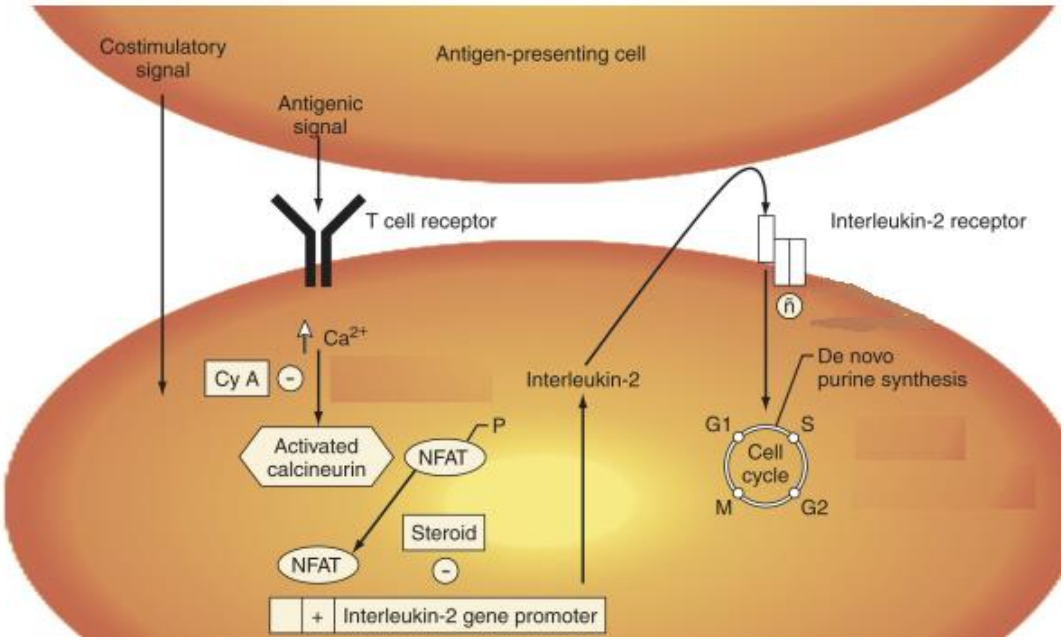


Figure 2.15 Mechanism of action of ciclosporin

Ciclosporin (CyA in diagram) blocks T cell receptors, inhibiting CD4 T cells and reducing expression of cytokines IL-2, IFN-γ, IL-3 and TNFα. Steroids pass through the cell membrane, bind to GCR and enter the cell nucleus where they inhibit the synthesis of pro-inflammatory cytokines IL-2, IFN-γ, IL-6 and TNFα, and promote the synthesis of anti-inflammatory proteins. (Denton *et al.*, 1999)

The metabolism of ciclosporin is carried out by the cytochrome P450 enzyme complex in the liver and co-administration of other drugs metabolised by this complex will lead to decreased bio-availability. Patient with liver disease may have impaired clearance of ciclosporin.

The main indications for use of ciclosporin are in the prevention of organ rejection in organ transplantation, graft-vs-host disease and other diseases with auto-immune components such as psoriasis, Behçet's disease, nephrotic syndrome, inflammatory bowel disease, type 1 diabetes and rheumatoid arthritis (Bach, 1989).

Initial studies in rheumatoid arthritis showed that ciclosporin was efficacious if used as monotherapy at a dose of 8-10mg/kg/day but similar effects with better ciclosporin tolerance can be achieved with doses of 5mg/kg/day when used in combination with low dose steroids (Johns & Littlejohn, 1999). In psoriasis, ciclosporin doses of 3-5mg/kg/day are efficacious, but relapses are common if treatment is stopped or reduced too quickly (Heule *et al.*, 1988). Possible causes of relapse seen after discontinuation of ciclosporin in autoimmune diseases could be due to insufficient control of the autoimmune response by the drug, inadequate

ciclosporin dose or administration, inappropriate reductions of ciclosporin dose or a sudden increase in the auto-immune response (Bach, 1989).

2.3.5 Ciclosporin adverse effects

Ciclosporin has been used in many conditions since 1985 and side effects associated to ciclosporin are well documented. Table 2.18, summarized from the Neoral (Novartis) clinical information booklet, shows the severity and frequency of adverse effects of ciclosporin as reported by Novartis in clinical trials in patients with organ transplantations, rheumatoid arthritis or psoriasis.

The most common adverse events seen with ciclosporin are hypertension, hypertrichosis, gingival overgrowth, headaches and electrolytes disturbances (Stein & Hanauer, 2000). Nephrotoxicity commonly seen with ciclosporin is dose-dependent and reversible. Serious nephrotoxic events have only been seen in patients treated for more than six months with greater than 7mg/kg/day (Feutren *et al.*, 1986). Hepatotoxicity is reported to occur in between 5% of patients (Lorber *et al.*, 1987). Hypertension induced by ciclosporin, whose mode of action is through an intracellular calcium binding protein, can be treated with a calcium antagonist such as nifedipine. Increased vulnerability to opportunistic fungal and viral infections also occurs secondary to immunosuppression. Ciclosporin is known to increase the plasma concentration of prednisolone. Other drug interactions are summarized in Table 2.19 .

Effect	Clinical presentation	Severity	Frequency		
			Organ trans-plantation	Rheumatoid Arthitis	Psoriasis
Nephrotoxicty	Increased Urea & Creatinine Acute (after 1st 2-3 weeks)	Mild, usually reversible	Common 25-38%	up to 48%	20%
	Haemolytic uraemia (after several weeks)	Severe , occ. reversible	Uncommon		
	Increased Urea & Creatinine, Proteinuria, hypertension Chronic	Severe, progressive	Uncommon		
Cardiovascular	Hypertension	Mild	up to 53%	up to 26%	27%
	Intravascular coagulation (e.g. DVT, renal artery/ vein thrombus)	Severe	Rare	<2%	
Neurotoxicity	Tremor, hyperaesthesia	Mild	up to 55%		
	Headache	Transient	up to 15%	up to 25%	16%
	Seizures	Severe	< 5%		
	Paraesthesia	Mild	3%	11%	7%
	Severe neurotoxicity	Related to toxicity	Rare		
Metabolic	Hyperkalaemia	Reversible	Common		
	Hyperuricaemia	Allopurinol Tx	Common		
	Hyperglycaemia	Reversible	Common		
	Hyperlipidaemia	Mild	Common		
	Hypomagnesaemia	Due to toxicity	Uncommon	<4%	
	Cramps	Mild	< 4%	up to 12%	
	Calcineurin inhibitor pain syndrome	Severe	Rare		
Gastroenterologic	Nausea, anorexia, diarrhoea	Mild/transien t	about 10%	up to 12%	up to 6%
	Abdominal discomfort	Mild	<7%	up to 15%	up to 6%
Hepatotoxicity	Increased transaminases, ALP, Bilirubin	Mild and transient,	< 7%		
Muco-cutaneous	Hirsuitism	Often severe	up to 45%	up to 19%	up to 7 %
	Gingival hyperplasia	Mild	up to 16%	<4%	up to 6%
	Facial dysmorphism	Infants	common		
	Acne, brittle finger nails	Mild	up to 6%		
	Decreased scalp hair	Mild	common	<4%	
Neoplastic	Lymphomas	Severe	< 6%		
	Skin cancers	Severe			
Infections	Urinary tract		21%	3%	
	Viral infections		16%	13%	10%
	Fungal infections (Localised)		7%		
	Wound and skin infections		7%		
	Pneumonia		6%	1%	
	Septicaemia		5%		

Table 2.18 Adverse effects of ciclosporin

(Adapted from Novartis leaflet- Appendix 3)

Action	Drugs involved	
Increase ciclosporin levels	Erythromycin Clarithromycin Chloroquine Ketoconazole Verapamil Diltiazen Grapefruit juice	Doxycycline Norfloxacin Cimetidine Metoclopramide Allopurinol Oral contraceptives
Decrease ciclosporin levels	Rifampicin Trimethoprim (IV) Phenythoin	Phenobarbitone Carbamazepine
Agents that increase nephrotoxicity	NSAIDS (care with high doses) Aminoglycosides	Co-trimoxazole Trimethoprim

Table 2.19 Drug interactions of ciclosporin

Appendix 4 considers, in detail, the use of ciclosporin in pregnancy, and concludes that ciclosporin in pregnancy appears not to pose a major risk to the foetus or the mother.

2.3.6 Ciclosporin in Leprosy Reactions

Ciclosporin in T1R

Given that ciclosporin selectively inhibits the activation of CD4 T cells and the expression of cytokines such as IL-2 and TNF-α, it was thought to be useful in the treatment of T1R. Three case studies have been reported (Table 2.20). Although the case reports were promising, no further research into the efficacy of ciclosporin was carried out because of the cost and problems with dose control with Sandimmune preparation. Sandimmune was the older gelatine preparation whose absorption was dependent on several factors including bile production, small bowel length, motility and mucosal integrity. A new micro-emulsion formulation (Neoral) was developed with significantly enhanced bioavailability compared to Sandimmune (Smith, 1996) and this was followed by an Indian generic version, Panimun Bioral, with similar pharmacokinetics to Neoral, but considerably cheaper (Gulati *et al.*, 1998).

Author, year, country	Patient	Dosage of ciclosporin	Outcome	Side effects
(Frankel *et al.*, 1992) **Holland**	Male 25 Filipino ,T1R , severe acne on prednisolone	20mg/kg/day for 8 months	No evidence of recurrence of T1R at 1 year after end of Tx	None reported
(Chin *et al.*, 1994) **Holland**	Male 78 Indonesian, T1R, had unstable diabetes	5-1mg/kg/day (reducing) for 9 months	Responded well, slower response of skin inflammation	None reported
(Chin *et al.*, 1994) **Holland**	Male 23, T1R, steroid induced cataract	5-1mg/kg/day (reducing) for 6 months	Responded well	None reported

Table 2.20 Case reports of ciclosporin use in T1R

With ciclosporin becoming more affordable, a pilot study was carried out assessing the efficacy of ciclosporin in severe T1R in Ethiopian and Nepali patients (Marlowe *et al.*, 2007) (Table 2.21).

Author, year, country	Type of study	Entry criteria	Number treated	Intervention	Outcome measures	Conclusion
(Marlowe *et al.*, 2007) **Nepal**	Open, prospective, uncontrolled	Severe acute T1R	8	12 weeks ciclosporin 5mg/kg and prednisolone 40mg for first 5 days	Skin signs, nerve score, improvement in clinical outcomes and relapse rates	75-100% improvement in all acute parameters, 67-100% maintained improvement, but 67% of acute sensory NFI relapsed after stopping treatment
(Marlowe *et al.*, 2007) * **Ethiopia**	Open, prospective, uncontrolled	Severe acute T1R	33	12 weeks ciclosporin 5mg/kg and prednisolone 40mg for first 5 days	Skin signs, nerve score, improvement in clinical outcomes and relapse rates	100% improvement in skin lesion and 50-60% improvement in nerve function but high levels of recurrence of reaction suggesting need for higher dose and longer treatment
(Sena *et al.*, 2006) **Brazil**	Open, prospective, uncontrolled	Chronic neuritis, not controlled by prednisolone	12	12 months reducing course starting at 5mg/kg/day	Sensory and motor function, nerve tenderness	All patients showed an improvement in sensory and motor function (decrease in the Clinical Severity Score), and absence of neuropathic pain in 11 out of 12 patients at end of treatment

Table 2.21 Clinical trials using Ciclosporin in T1R

*Ciclosporin increased to 7.5mg/kg/day if deterioration

In the Ethiopian part of the study, performed in ALERT Hospital, Addis Ababa, ciclosporin was given to 33 patients with T1R for three months in a dose range of 5-7.5mg/kg/day. This led to improvements in skin lesions in 85% of patients and 45% of patients had improvement in nerve pain and tenderness. Sensory nerve impairment improved in 45% of Ethiopian patients and motor function impairment in 53% of patients. Almost 88% of Ethiopian patients needed the higher dose of ciclosporin to show improvement partly because of the severity of the reaction. The study showed that in those patients treated with high-dose ciclosporin, 53% of patients with sensory impairment and 60% with motor impairment improved. A few Ethiopian patients with chronic NFI responded to ciclosporin. This was an encouraging result as in many leprosy endemic countries patients present late with chronic NFI. Almost 70% percent of Ethiopian patients developed new signs of reaction after stopping treatment, suggesting that they would benefit from a treatment period longer than three months.

In the Nepali study, eight patients treated with ciclosporin were compared to a similar group of patients treated with prednisolone. Improvement in skin lesion was at 87.5% in the ciclosporin group compared to 74% in the prednisolone group. Similarly the ciclosporin group showed 83% improvement in sensory testing compared to 22% in the prednisolone group.

The results of the above studies were encouraging as it appeared that ciclosporin monotherapy may be an effective alternative treatment in prednisolone-resistant or prednisolone-dependent cases of T1R. The study recommended using higher doses of ciclosporin (7.5mg/kg/day) in future studies, longer periods of treatment, as well as tapering the drug slowly or adding low dose prednisolone to prevent relapse.

Few ciclosporin side effects were seen in the two clinical trials conducted in T1R (Marlowe *et al.*, 2007). Of the 33 Ethiopian patients, three developed hypertension; this was easily controlled with anti-hypertensive therapy and did not necessitate stopping ciclosporin treatment. Of the ten Nepali patients one developed jaundice (possibly dapsone related), two developed raised serum creatinine levels (one responded to decreased ciclosporin dosage and the other was removed from the trial as his T1R features worsened. Two other patients developed mild side effects (loss of appetite and indigestion controlled with antacids), but continued their ciclosporin with no further adverse events.

Ciclosporin in ENL

Ciclosporin has been tested in vitro in ENL (Uyemura *et al.*, 1986), where it was found to restore the activity of T suppressor cells and inhibit IL-2 production. Ciclosporin has also been used successfully in the management of ENL in a small case series suggesting that it could be an effective alternative to steroids (Table 2.22).

Author, year, country	Patient	Dosage of ciclosporin	Outcome	Side effects
(Miller *et al.*, 1987) **USA**	Male 38 Filipino, ENL, uncontrolled on steroid and thalidomide	10mg/kg/day for 8 months	Responded well, with decreased need for steroids and decreased recurrence	None
(Miller *et al.*, 1987) **USA**	Male 51 Vietnamese, ENL, uncontrolled on steroid and thalidomide	10mg/kg/day decreased to 6mg/kg/day For 8+ months	Good response, with no need for steroids after initial weaning and no recurrence	Watery stool and abdominal pains on higher dose
(Miller *et al.*, 1987) **USA**	Woman 31 Filipino, ENL uncontrolled on steroid, thalidomide and azathioprine	7mg/kg/day	Improved neuralgia and poly-arthralgia but persistence of cutaneous nodules - ? sub-optimal dosage	Watery stool and abdominal pain on trials of increased dose

Table 2.22 Case reports of Ciclosporin use in ENL

In view of the above results, and the need for a non-teratogenic alternative for the management of ENL, it was thought that doing pilot studies to assess ciclosporin's efficacy in ENL would be valuable.

CHAPTER 3 MEASURING REACTION SEVERITY

Validating the Clinical Severity Scale for T1R in Ethiopian leprosy patients

- **Methods**
- **Results**
- **Conclusion**

Preliminary work to develop a severity grading tool for ENL

- **Methods**
- **Results**
- **Conclusion**

A tool which enables clinicians to assess the severity of leprosy reactions would be useful in defining outcomes in clinical trials. Measurement obtained through a validated scale would also empower researchers with a very useful instrument with which to be able to compare their results. It is precisely this lack of uniformity surrounding interpretation of data that has hindered development of internationally accepted treatment protocols and guidelines, while also making trialling of new therapeutic agents difficult. A validated clinical severity scale for leprosy reactions would significantly improve research quality and provide a tool to promote uniformity and comparability of research.

A severity scale for T1R has been developed and validated previously, and the validation exercise in Ethiopian patients is described here. The initial steps taken to develop a new severity scale for ENL are also described in this chapter.

3.1 VALIDATING CLINICAL SEVERITY SCALE FOR T1R IN ETHIOPIAN PATIENTS

The validated Clinical Severity Scale for T1R consists of 21 items to assesses three components of T1R (Walker *et al.*, 2008). The first section looks at skin involvement using number of affected lesions, the degree of inflammation and the presence of peripheral oedema (Score A). The second section is a measurement of sensory function of the nerves by using Semmes-Weinstein monofilaments to assess sensation in the hands and feet, and cotton wool for corneal sensation (Score B). The third section uses a standard measure of muscle power (MRC grading) to assess the motor function of the nerves of the face, hands and feet (Score C). The sum of the total for each section (A, B, and C) gives the overall severity scale score with a range of 0-63 (Appendix 1). The maximum score possible for sections A, B and C are 9, 24 and 30 respectively. A mild T1R is characterised by a score of 4 or less; a moderate T1R by a score between 4.5 and 8.4 and a severe T1R is a score of 9 or more.

The Clinical Severity Scale for T1R was validated in Ethiopian patients before using it in our ciclosporin clinical trials.

3.1.1 Methods

A sample size of 81 patients was used in the validation study of the T1R Severity Scale (Walker *et al.*, 2008). Patients presenting with signs and symptoms of T1R at the Leprosy Clinic at ALERT Hospital in Addis Ababa were recruited between February 2010 and August 2010. All patients gave informed consent to participate in the assessment. Patients were examined independently by a health worker who was trained to use the scale and by an experienced leprologist who categorized the reaction as mild, moderate or severe. Neither assessor was aware of the result of the others examination. Inter observer reliability was not tested in this case because of insufficient members of staff allocated to the clinic.

The results were entered into an Access database and the data was analysed using the Statistical Package for Social Sciences (SPSS version 20).

3.1.2 Results

135 patients with T1R were examined using the T1R severity scale assessment sheet (Appendix 1) by a trained leprosy health worker, and reviewed by the specialist to grade the severity of the reaction, on the same day. Patients could be presenting with new T1R or be on treatment for T1R.

The severity of the T1R was categorised by the specialist as mild in 43 (32%), moderate in 34 (25%) and severe in 38 (28%) patients. Another 20 patients (15%) with no signs of active T1R but on prednisolone treatment were assessed. Median scores for each category were none=0 ± 1.69; mild= 3.0 ± 2.55; moderate= 6.5 ± 2.55 and severe= 19.0 ± 9.70. The box-plot in Figure 3.1illustrates the score distribution clearly.

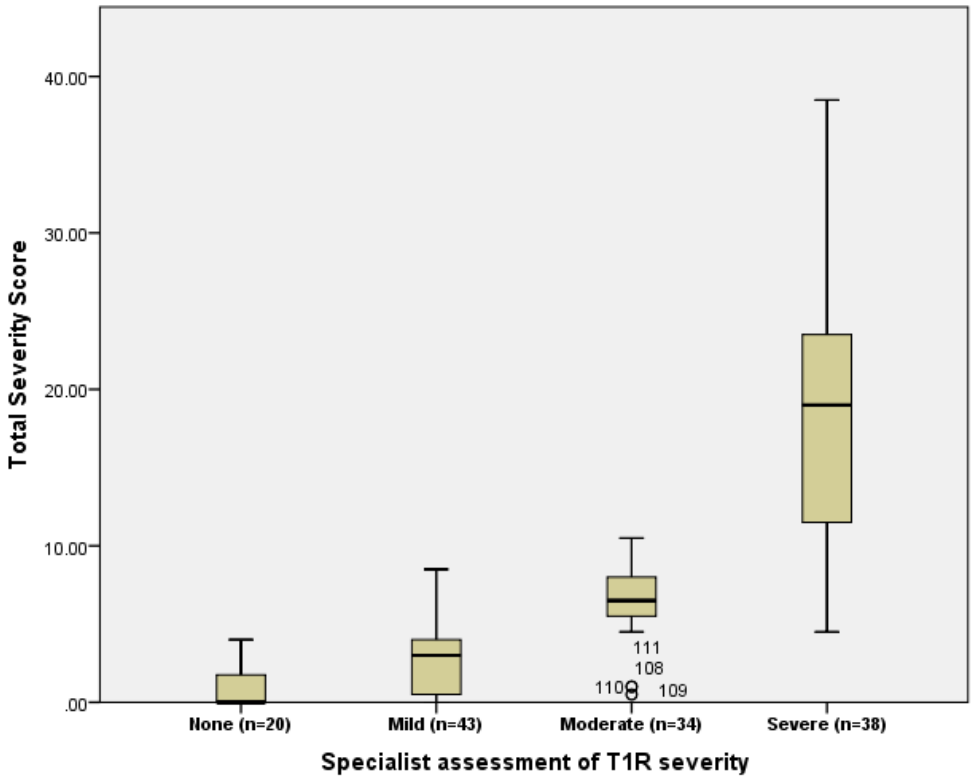


Figure 3.1 Box plot of Reaction Severity Scores by specialist severity classification showing medians, interquartile ranges and minimum and maximum scores.

The differences in the scores between the group with no active reaction and the mild group, the mild group and the moderate group and the moderate group and the severe group were all statistically significance ($p < 0.001$). The group of patients graded as having severe TIR had the widest confidence interval, and there is an overlap between each category.

3.1.3 Conclusion

This study showed that the Clinical Severity Scale is a valid tool for assessing the severity of T1R in Ethiopian patients and could be used to measure reaction severity of T1R in the ciclosporin trials.

The reliability of the tool could have been tested by doing a further inter-observer validation exercise but it was felt that due to limitations in clinic staff this was not essential.

3.2 PRELIMINARY WORK TO DEVELOP A SEVERITY GRADING TOOL FOR ENL

The few published scales available in the literature constructed for the purpose of measuring ENL severity have the problem of differing significantly in their approaches of assessment (i.e. categorical vs. dimensional conceptualization) and content validity. Authors applying the categorical model abide to the simplistic idea of merely considering whether a condition is present or not. This "all or nothing" approach overlooks the fact that in medicine most variables follow a continuum. The dimensional model on the other hand defends the basic idea that the more finely something can be measured the better. In this model, a continuous measure of severity is applied by using a severity scoring system for ENL. Thus, ENL patients´ symptoms fall along the severity dimension in terms of how much of the attribute they have.

The published scoring systems reviewed were not thought to be useful for comparison within a clinical research study, for monitoring change in a patient and for comparison across clinical studies. None had been validated, some had a large subjective component, some took account of response to treatment, and in most, the importance of various systemic features was not defined. Preliminary work to develop an ENL severity scale was done as part of the ENL ciclosporin trials.

3.2.1 Methods

Expert opinion

To establish content validity, a questionnaire was distributed to doctors working in leprosy at an ENL workshop in Cebu, Philippines in 2012. The questionnaire used open-ended questions to assess the signs of ENL that they would include when measuring severity and how they categorised severity.

Scale development

A preliminary exercise to collect ENL data was conducted in the Leprosy Clinic at Addis in order to identify important features of ENL that should be included in a scale.

The data collecting tool was adjusted once the responses of the leprologists were analysed and a final data collecting tool was included in the trials of Ciclosporin in ENL (Appendix 5).

The form had three parts: questions on symptoms of ENL, a section on clinical findings related to ENL and a malaise scale of 1-5 using Wong-Baker faces to record the patient's perception of "un-wellness" associated to ENL. Patients were examined independently by the study physician who had received previous training to use the scoring system and then by an experienced leprologist who categorized the reaction as mild, moderate or severe. Neither assessor (nor the patient) was aware of the results of the other's examination.

The data were entered into an Access database as part of the Ciclosporin studies, and was analysed using the Statistical Package for Social Sciences (SPSS version 20).

The results were looked at according to the different severity categories allocated by the specialist physician to identify the clinical features of ENL which were markers of severity.

3.2.2 Results

Expert opinion

The questionnaire was completed by eleven leprologists from Asia, Brazil, Ethiopia and the UK with a total of 206 years (mean 18: 5-40 years) of experience in managing ENL. Four questions were asked in order to assess which clinical features of ENL are indicators of severity.

Question 1: *What clinical signs would be important to include in an attempt to objectively measure ENL reaction?*

The answers are shown in descending frequency in Table 3.1.

Important signs of ENL	Number (n=11)
Systemic features	7
Fever	7
Nodules	6
Arthritis	5
Nerve pain or NFI	5
Eye involvement	5
New skin lesions	4
Ulcerated nodules	4
Lymphadenopathy	4
Necrotic nodules	3
Tender skin lesions	3
Orchitis	3
Renal involvement	3
Co-morbidities (infection, diabetes	3
Pustules	2
Malaise	2
Bone pain	2
Laboratory parameters	1
Oedema	1

Table 3.1 Important signs of ENL – expert opinion

Question 2: *How would you measure these signs?*

ENL nodules should be clinically assessed by the number, distribution, tenderness, presence of ulceration and necrosis. The presence and number of systemic features were considered important by many. The degree of fever was considered important and one suggestion was given to use three categories of temperature: under 37.5˚C, between 37.6- 39˚C and above 39˚C (associated with chills and rigors). A patient perception scale was suggested to measure malaise. The presence of oedema was mentioned by four leprologists as being an important clinical finding. Laboratory parameters measuring leucocytosis, ESR, CRP, liver function and urine albumin were suggested.

Question 3: *Which signs, if any, are more likely to indicate a more severe ENL reaction?*

Severity was ENL was thought to be indicated by the presence of ulcerated lesion and a high number of systemic features by more than half of the specialist. High grade fever and eye involvement followed closely. Number of nodules, although an important feature of ENL, was only mentioned as a marker of severity by four

leprologists. Poor response to treatment and recurrence of ENL were mentioned by two of the specialists (Table 3.2).

Signs indicating more severe ENL	Number (n=11)
Ulcerated lesions	6
A high number of systemic features	6
High grade fever	5
Eye involvement	5
Numerous nodules	4
Necrosis	4
Oedema	4
Nerve pain	4
Painful lesions	3
Vesicular/bullous lesions	2
Arthritis	2
Abnormal lab results (WCC/ESR)	2
Hepatitis	1
Not responding to treatment	1
Recurrence of ENL	1
Acutely ill patient	1
Dactylitis	1
Renal involvement	1

Table 3.2 Signs indicating severe ENL - expert opinion

Question 4: *How do you categorise the severity of ENL reaction?*

Ten leprologists selected the categorisation of mild, moderate or severe, with three also selecting to add the steroids required or not required. One leprologist suggested the categorization of mild versus severe.

Scale development

31 individuals were recruited with ENL, with an average age of 35. There were 25 men and 6 women. 74% had lepromatous leprosy and 37% had a BI higher than 4 at the time of presentation with ENL. Patient data are presented in Table 3.3 according to the severity grading given by the specialist clinician.

A larger proportion of patients with severe ENL had a BI≥4 (56%) compared to those with moderate or mild ENL. Sixteen patients were on prednisolone when examined to grade their ENL severity.

	Mild n=6	Moderate n=9	Severe n=16
Age average	38.5	31.3	35
R-J % of LL	67%	78%	75%
BI high ≥4	33%	22%	56%
Average number of acute episodes	4	7.2	5.1
On prednisolone at ENL presentation	33%	55%	50%

Table 3.3 Patient characteristics according to specialist ENL severity category

Patients with severe ENL had twice the number of days of being unwell prior to presentation (12 vs 6). A larger proportion of patients in the severe category and presented with their first ENL episode and the delay in presentation may be explained by the fact that the patient was not aware of the condition and had possibly been misdiagnosed at a Health Centre. Patients who have recurrent and chronic ENL tends to seek medical assistance faster and know to come to the leprosy clinic.

Patient history and symptoms	Mild n=6	Moderate n=9	Severe n=16	Chi-Square *p* value
Mean number of days unwell	6	6.4	12.37	
Patient perception of pain (average score)	2	2.7	3.9	0.105
New lumps/lesions	100%	100%	100%	1.00
New sensory loss	0%	55%	56%	0.52
New weakness	0%	45%	75%	0.008*
New tingling	33%	78%	69%	0.196
New pain in joints	33%	55%	69%	0.332
New pain in bones	15%	45%	75%	0.042*
New pain in testicles	0%	14%	1%	0.282
Painful eyes	33%	55%	31%	0.478
Visual disturbances	15%	33%	12%	0.453

**p value significant at <0.05*

Table 3.4 Patient symptoms according to specialist ENL severity category

Patient symptoms on the day of examination are presented in Table 3.4. All patients had new nodules as a clinical sign. Patients classified as having moderate or severe ENL showed increased NFI. Increasing proportion of patients had pain in joints and bones as the severity grading increased. A higher number of patients in the moderate category had pain in the testicles or eye symptoms. New weakness and bone pain where the only two features to show a significant difference between severity categories.

Table 3.5 describes the clinical findings on examination per severity category. Number of ENL lesions increased with severity, and patients categorized as severe had nodules than were inflamed enough to affect function and 25% had developed ulceration in the nodules.

Clinical signs		Mild n=6	Moderate n=9	Severe n=16	Chi-Square *p* value
Number of ENL lesions	1 to 5	100%	33%	19%	0.067
	6 to 20	0	45%	44%	
	>20	0	22%	37%	
Inflammation in ENL lesions	None	0	0	0	0.018*
	Erythema and pain	100%	100%	56%	
	E & P plus function affected	0	0	19%	
	Above plus ulceration	0	0	25%	
VMT decrease		0	11%	50%	0.039*
ST decrease		15%	33%	44%	0.493
Nerve tenderness		0	67%	75%	0.008*
Tibial tenderness		33%	67%	81%	0.029*
Oedema		0	78%	100%	0.001*
Dactylitis		0	33%	50%	0.091
Lymphadenitis		0	11%	56%	0.061
Testicular tenderness		0	14%	0.60%	0.193
Fever		0	33%	50%	0.98
Proteinuria		0	0	19%	0.125
Red eyes		15%	45%	31%	0.537

**p value significant at <0.05*

Table 3.5 Clinical findings in patients according to ENL severity category

Nerve tenderness and NFI appear to be markers of severity as do tibial tenderness, oedema, dactylitis and lymphadenitis. Temperature was recorded with an ear thermometer and fever was defined as a temperature above 37.5˚C. Fever was present in 50% of patients with severe ENL and 33% of patients with moderate ENL. Proteinuria, tested with a urine dipstick was positive in only 19% of patients categorized as severe ENL. Again testicular tenderness was more common in the moderate ENL group as were inflamed eyes. Patients with eye symptoms were reviewed by the hospital ophthalmologist: seven were diagnosed as having conjunctivitis, one blepharitis and one episcleritis. The clinical features that showed statistically significant difference between severity categories were degree of

inflammation in the ENL lesions, a decrease in motor function, nerve tenderness and tibial tenderness.

3.2.3 Conclusion

Eleven leprologists were interviewed in order to establish content validity for a future grading system for ENL severity. A data collecting form based on the information collected was designed and 31 patients were recruited in the initial pilot study to assess markers of severity for ENL. Markers of severity that were statistically significant were the degree of inflammation in ENL nodules, motor function impairment, bone pain/ tenderness and nerve tenderness. These were different from the leprologists' choice of markers of severity which were degree of inflammation of ENL lesions, number of systemic features present, fever, eye involvement, followed by number of nodules, oedema and nerve pain.

The data collecting form was readjusted in two areas of nerve function assessment that were noted to cause confusion. The level of nerve function impairment was made more precise by asking for recent (less than 6 months duration) nerve function impairment or if a previous VMT/ST assessment was available in the clinic records, then a decrease from the previous assessment results was recorded.

The re-adjusted data collecting sheet and specialist's grading of severity were both included in the clinical trial documentation in order to gather as much data as possible to suggest a future severity scale for ENL.

CHAPTER 4 QUALITY OF LIFE MEASURE

Introduction to Quality of Life Questionnaires

The use of Quality of Life Questionnaires

Developing questionnaires

Adapting and using questionnaires

Quality of life instruments used in Leprosy

Choosing a HRQoL questionnaire for leprosy patients in Ethiopia

SF-36 HRQoL in Ethiopia

Developing and validating the Amharic SF-36 HRQoL in leprosy patients in Ethiopia

Amharic SF-36 in leprosy patients

Discussion.

4.1 INTRODUCTION TO QUALITY OF LIFE QUESTIONNAIRES

Quality of life as an outcome measure is increasingly being included in clinical trials worldwide, but it has so far been rarely used in leprosy clinical trials. We were keen to use a quality of life questionnaire in our study to reflect the patient's assessment of the treatment. Choosing and validating the most appropriate tool is presented in this chapter.

4.1.1 The use of Quality of Life Questionnaires

In recent years there has been a broadening of focus in measurement of health, beyond traditional health indicators such as mortality and morbidity, to include measures of the impact of disease and impairment on daily activities and behaviours, perceived health measures and disability/functional status measures. To better understand the consequences of chronic conditions on patients' lives and to evaluate the benefit of new treatments, researchers are developing more meaningful end-points based on patients' perceptions. Quality of life has now become an indispensable outcome measure in many randomized clinical trials and other studies. It provides the patient's voice in measuring health improvement or decline and assessing treatment effectiveness.

The term "quality of life" is used to evaluate the general well-being of individuals and societies. The term is used in a wide range of contexts, including fields of international development, health care and political science. Standard indicators of quality of life include physical and mental health, education, recreation and leisure time, social belonging, employment, wealth and spiritual wellbeing. Health-related quality of life is a more specific term to emphasize the focus on the effects of disease and its treatment. It usually encompasses eight health domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. Patient-reported outcome questionnaire is another term used to describe quality of life measurements in health.

Generic health-related quality of life instruments (HRQoL) are designed to be applicable across a wide range of diseases, different populations and medical interventions. Disease-targeted measures, in contrast, are designed to be relevant to a

particular disease such as diabetes or rheumatoid arthritis. Disease-targeted measure have the potential to be more sensitive to smaller differences and smaller changes over time than generic measures, because they are selected to be particularly relevant to a given condition. Rather than advocate using only one or the other, the most typical recommendation is to supplement a generic measure with disease-targeted items (Patrick & Deyo, 1989).

In clinical trials, a targeted measure may provide more detailed outcome information regarding changes in the particular patient population. In addition, targeted measures may be perceived as being more relevant to patients, clinicians and researchers (Guyatt *et al.*, 1993). However, use of both targeted and generic measures may be optimal in most clinical trials. By using only a targeted measure, the general or overall impact on functioning and well-being may be missed.

4.1.2 Developing questionnaires

In the past, the items to include in many quality of life questionnaires were determined by a review of the literature and of the content of existing instruments. Developing a new quality of life instrument with content relevance to patients needs to be done incorporating the views of affected patients via individual interviews and or focus groups. Once the content is generated, pre-testing and expert analysis are necessary.

A HRQoL measurement needs to be reliable and valid. Inter-rater reliability refers to the extent to which a measure yields the same number or score each time it administered, all other things being equal (i.e. true change has not occurred in the attribute being measured). Reliability is also defined in terms of internal consistency as reflected in a measure of overall correlation between scale items. Reliability of scale measurements is linked to the Classical Test Theory (Spearman, 1904) which suggests that any assessment will only reveal an individual's score, and that this is not always reflective of their "true" score, as there is always something in the environment that impacts an individual's performance. These include uncontrollable or random effects referred to as error. Five different measures are used to quantify scale reliability:

1. Consistency of same test over time (Test-retest reliability which can be affected by actual change over time and memory)
2. Consistency over alternative test forms (Alternative forms reliability)
3. Consistency across items within a test (Internal consistency- measured using Cronbach's alpha)
4. Inter-rater reliability (Same test done by two interviewers)
5. Intra-rater reliability

Validity is the degree to which the measure reflects what it is supposed to measure rather than something else. The distinction between reliability and validity is important because a measure may be reliable (i.e. yielding the same score for the same patient), but it may be consistently measuring the wrong thing. To infer validity the following kinds of evidence are generally used: content validity, criterion validity, construct validity and responsiveness to change. Further evaluation of questionnaire item and scale properties would need to be done by applying item response theory modelling in the form of Rasch Analysis.

In any given context it is important that a scale has proven reliability and validity.

4.1.3 Adapting and using questionnaires

Due to the international nature of clinical research, the need for cross-culturally valid patient reported outcomes questionnaires has grown considerably. For cross-cultural clinical research, the ultimate goal is to pool data across languages in order to evaluate the effect of treatment on an outcome measured by the same questionnaire. To achieve this objective, for each language, the concepts assessed by each item should be as identical as possible, the aggregation of items should result in the same constructs and the metric scales should be similar.

When a questionnaire has already been developed and used in one culture, the sequential approach based on a thorough translation is essential for controlling potential bias at the level of the item. Many translation guidelines have been published and most describe a forward-backward translation by a qualified team, followed by pilot testing with patients. This assumes that the constructs of a questionnaire, and their content, are relevant and equivalent across cultures.

A different approach to creating multiple language questionnaires has been used in the questionnaire development phase. At this stage, it would be possible to use the parallel approach or simultaneous approach where major cultural issues in concepts are addressed before item generation. Development of the questionnaire is based on common, culturally relevant concepts and on patient wording in different languages.
A valid and precise measurement tool is developed by creating an item bank (i.e. a collection of relevant questions, and their rating scales, that contribute information on the position along the continuum defined by the item). Items are then tested by the Item Response Theory or the faster computerized adaptive testing (CAT).
Responses to subjective questions, such as those concerning quality of life, are open to external influences, and a patient may answer the same question very differently according to the context. For example, the setting (home or hospital) or mode of administration (self-administered, interview, telephone-based) might have an impact. The order of the questions might influence answers by focusing attention on specific issues or by affecting the patient's mood. Lengthy questionnaires may lead to boredom and responses being left out. Proxy respondents, either health professionals or relatives, may rate items differently from what the patient would have done. These are all factors to be taken into account not only to get a good response rate but also to minimize errors. Longitudinal studies need clear assessments points decided on from the outset (e.g. start of the clinical trial, mid-way and at the end), and greater attention to minimizing missing data. Preventing missing data requires careful study planning and protocol development, appropriate data collection forms, trained study personnel with a positive attitude and explicit follow-up procedures. Interpreting minimally important differences or changes in HRQoL scores and considering the meaning of these differences is important.

4.2 QUALITY OF LIFE INSTRUMENTS USED IN LEPROSY

With comparative clinical studies being conducted in the management of leprosy reactions, leprosy related quality of life questionnaires can allow patients' assessment of treatments to be taken into account.

To select the most appropriate HRQoL questionnaire for our Ciclosporin in Leprosy Reaction study, we looked at published leprosy studies that had already used a QoL instrument. A publication search in January 2011 and October 2011, on Pub-med and Medline, using search terms: leprosy and quality of life, resulted in only six published quality of life studies with leprosy patients. Three of these used WHOQOL-BREF, two the DLQI and one the SF-36.

WHOQOL-BREF

The WHOQOL-BREF, developed in 1991 by the WHO, is a shortened version of the original WHOQOL-100 (often used in mental health related surveys), looking at the following domains: physical health, psychological health, level of independence, social relationships, spiritual and environmental conditions. It was developed simultaneously in 15 field centres around the world and available in 20 languages. The WHOQOL-BREF comprises 26 items and is more convenient for larger studies and clinical trials. It is an international cross-culturally validated quality of life assessment instrument (WHO, 2012c).

A study in India used a version of WHOQOL-BREF (exact questions not published) made up of 33 questions, i.e. seven extra than items that the WHOQOL-BREF, to compare quality of life between 50 patients affected by leprosy and 50 patients without leprosy (Joseph & Rao, 1999). The mean QOL score of the cases was significantly lower than that of the controls with the exception of the spiritual domain. The mean total score for women was higher than that of males in each domain and age group. Males with deformities had a significantly lower score than those with no visible deformities. Although the scores for females with deformities were also lower than those without deformities, the differences were not statistically significant.

Another study, in Bangladesh, compared the quality of life between 189 leprosy patients and 200 patients with other chronic diseases using the WHOQOL-BREF, (Tsutsumi *et al.*, 2007). It concluded that lower QOL in leprosy patients was linked to the presence of perceived stigma, fewer years of education, the presence of deformities, and a lower annual income.

The most recent study was from India, in which the WHOQOL-BREF was used to compare the QoL between 51 leprosy patients and 58 community members. The mean quality of life scores was significantly lower in the leprosy patients in physical

and psychological domain but not in the social relationship and environmental domain. Males scored less in each domain as compared to male control group but the difference was not significant except in the physical and environmental domain. Female leprosy patients scored less in each domain compared to female control group and the difference was not significant except in the psychological domain (Mankar *et al.*, 2011).

DLQI

The DLQI, the Cardiff Dermatology Quality of Life Index, consists of ten questions, designed to assess the effect of a range dermatological conditions on quality of life in adults. It covers several dimensions of life quality, including pain, embarrassment, interference with activities, and social and sexual relationships. It has been used in at least 36 skin diseases and translated into 21 languages, including Amharic for a study involving podoconiosis patients in Ethiopia (Henok & Davey, 2008). The questions in the DLQI are all skin related and do not cover nerve damage and disability caused by leprosy.

A Chinese study assessed QoL, with the use of the DLQI, finding that the 64 patients with lepromatous leprosy (an often disfiguring type of leprosy) interviewed had a significantly lower QoL than the 64 controls (healthy volunteers or patients with other dermatoses) (An *et al.*, 2010).

The DLQI was also used in a Brazilian study comparing the quality of life in leprosy patients in two different socio-economic settings. QoL was found to be impaired in 76.9% of the 26 patients from rural Amazonia compared to 19% of the 21 patients from urban Sao Paolo versus (Proto *et al.*, 2010).

SF-36

The Short Form-36 Health Survey (SF-36) is a HRQoL instrument consisting of 36 items assessing eight health concepts using multi-item scales, and administered using a past four weeks reporting interval (Ware, 1993) . It has been translated into various languages and is now widely used in more than 40 countries.

An observational study from Brazil using the SF-36 in 107 leprosy patients was published in October 2011 (Lustosa *et al.*, 2011). A correlation was found between a low QoL score and late diagnosis, multibacillary forms of leprosy, reactions,

disability diagnosis grade-2, and prejudice. There was no comparison group in this study.

Other scales have been used in leprosy studies, mainly to measure functional limitation, activity limitation and social participation of patients. They have sometimes been us to reflect quality of life. They are described below:

A. SALSA (Screening of Activity Limitations and Safety Awareness): this tool was developed and validated in five countries as a method of measuring activity limitation and awareness of risk in patients affected by leprosy and diabetes (both patient groups being at risk of peripheral neuropathy). It is a short questionnaire (20 items), administered in ten minutes, which can be used to compare groups of individuals in different countries or to assess change in the same person or group over time. SALSA can also be used as a screening instrument by general health workers in order to select patients for referral to specialist centres (Ebenso *et al.*, 2007). It has been found to be reliable in the Hausa version on leprosy in Nigeria (Ebenso & Velema, 2009) and has also been used in Brazil (Barbosa *et al.*, 2008), in the Philippines (Boku *et al.*, 2010) and in Bangladesh (van Veen *et al.*, 2011).

B. Participation scale: was developed and validated as a scale to measure social participation for use in rehabilitation, stigma reduction and social integration programmes in people affected by leprosy or disability. The scale development study was done in Nepal, India and Brazil (van Brakel *et al.*, 2006). It is an 18-item instrument in which respondents rate their participation in comparison with a "peer". It can be used to collect data and impact of interventions to improve social participation. It may be used to compare data between clients, interventions and programmes. It has been used in a study in Brazil with ex-leprosaria patients (Lesshafft *et al.*, 2010).

C. EHF (Eyes Hands and Feet) score: is an instrument to measure functional limitation. It has been developed gradually over 70 years by the WHO with the present tool finalized in 1988 and revised more recently (Brandsma & Van Brakel, 2003). Its main use has been in reporting disability level at leprosy diagnosis and more recently it has been used as an indicator for early case detection and as an indicator of change in impairment for patients while on treatment. The individual scores for eyes, hands and feet can be added to obtain the EHF sum score.

4.3 CHOOSING A HRQOL QUESTIONNAIRE FOR LEPROSY PATIENTS IN ETHIOPIA

The first choice of HRQoL instrument for our leprosy study had been the WHOQOL-BREF (WHO) (Appendix 6). As an international cross-culturally validated quality of life assessment instrument, with an Amharic version already translated and used by the Addis Ababa University, it seemed the ideal instrument (Appendix 7). However, the WHO website did not report an official Amharic translation and multiple email enquiries to the WHOQOL team in Geneva went unanswered. The Psychiatry team at Addis Ababa University had translated and used an Amharic version of WHOQOL-BREF but there were no comments on validation (Araya *et al.*, 2007). The available translation also had 7 extra questions about stigma and social integration. WHOQOL-BREF in Amharic had been used in an assessment of 749 women displaced by conflict (Araya *et al.*, 2011), and later in an assessment of 346 patients affected by podoconiosis versus 349 healthy individuals (Mousley *et al.*, 2013).

During a pilot study with 12 leprosy affected patients at ALERT, the WHOQOL-BREF questionnaire was found to be "too general" with some difficult to interpret questions for that specific patient group and very few questions relevant to their disease.

Some of the difficult questions for this patient group are discussed below.

Question 1: *"How would you rate your quality of life?"*

The concept of 'quality of life' was very difficult to bring across and despite short explanations, it was often mixed up with social class, wealth and effort used into survival.

Question 6: *"To what extent do you feel your life to be meaningful?"*

Much clarification was needed for this question and brought in the concept of suicide which is taboo in Ethiopia and patients regarded this question as a test of their faith rather than the feeling of a meaningful life.

Question 8: *"How safe do you feel in your daily life?"*

Most patients interviewed had arrived from distant rural areas for the first time and were tested not only by the journey but also by the conditions in a large city where people speak a different dialect. Most patients, unable to afford accommodation, had

slept rough, and were only able to discuss the perils of the present journey, thus finding choosing a specific answer difficult.

Question 13: *"How available to you is the information that you need in your day-to-day life?"*
This question brought up further questions about its value. Patients being in the majority poorly literate relied on neighbours and friends for information.

With poor patient response in our pilot study, we decided to look for an alternative HRQoL tool.

Alternative to WHOQOL-BREF: SF-36

The Short Form-36 Health Survey (SF-36) was originally developed as a way of measuring the outcome of different types of healthcare delivery in the United States (Ware, 1993) (Appendix 8). The SF-36 can be self-administered or it can be used by an interviewer to solicit the information. It takes about 5 to 10 minutes to complete. It comprises 36 items assessing eight health concepts using multi-item scales, and administered using a past four weeks reporting interval:

1. Physical functioning (10 items)
2. Role limitations caused by physical health problems (4 items)
3. Role limitations caused by emotional problems (3 items)
4. Social functioning (2 items)
5. Emotional well-being (5 items)
6. Energy/fatigue (4 items)
7. Pain (2 items)
8. General health perception (5 items)
9. Perceived change in health during the last 12 months

The relationship between these domains is shown in Figure 4.1. Two summary scores can be calculated: a mental health component summary score (MCS) and a physical health component summary score (PCS).

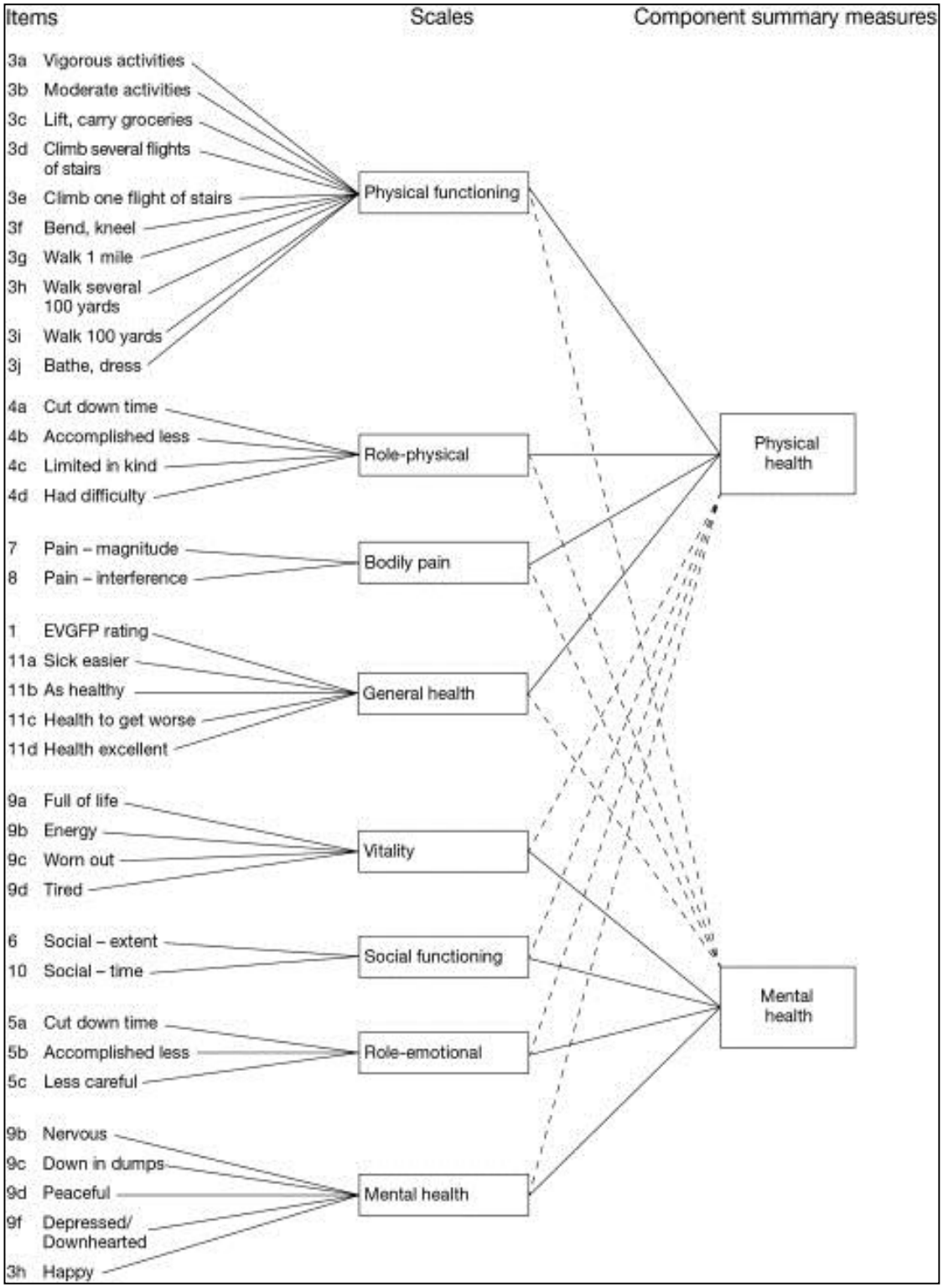


Figure 4.1 SF-36 v2 Health Survey Measurement Model

The SF-36 is used to compare the relative burden of disease for different groups of patients (e.g. diabetes vs. hypertension vs. depression) as well as comparing the progress over time with or without treatment. Meaningful and valid comparisons of different groups assume that the generic measure is equivalent in different groups.

This means that the health related quality of life scales should have the same level of acceptability, reliability and validity in different segments of the population, with attention being paid to evaluating cross-group equivalence involving different language or race/ethnic subgroups.

Although cross validation of item selection and scoring of SF-36 has been done (Gandek *et al.*, 1998b), this has often been done on patients living in developed countries with similar standards of living. At first glance, the face validity of some SF-36 items appear questionable for patients in low-income settings, such as questions about "playing golf", "bowling", "pushing a vacuum cleaner" and "climbing several flights of stairs" in a country where few buildings have several floors. This observation pointed to a need to explore the construct validity of the SF-36 before adopting it for use with leprosy patients in our study in Ethiopia.

We considered the possibility of using a validated shorter version of SF-36, the SF-12, and adding leprosy specific questions to develop a disease-targeted HRQoL measures for leprosy but the amount of work involved in creating this was beyond the scope of this study. After much consideration, the SF-36 was chosen as the tool to assess health related quality of life in the clinical trial comparing ciclosporin and prednisolone in the management of leprosy reactions.

4.4 SF-36 HRQOL IN ETHIOPIA

A literature search done in October 2011, on the use of SF-36 in Ethiopia, found only four publications. A team at Addis Ababa University, Public Health Department published a study in the Ethiopian Medical Journal (Kebede *et al.*, 2004) in which the SF-36 was translated into Amharic, used in a general health survey in 1990 rural people to establish general population norms for various sex and age groups and to describe the effects of socio-demographic factors on SF-36 scores. It concluded that the Amharic SF-36 had acceptable psychometric properties and construct validity. It was later used to assess quality of life in 271 patients with schizophrenia (Kebede *et al.*, 2005) and 315 patients with bipolar disease (Kebede *et al.*, 2006). A more recent study, conducted in Ethiopia, showed that the Amharic version of SF-36 was a valid and reliable health survey instrument to assess the quality of life of 420 people living with HIV and on HAART (Abera *et al.*, 2010).

Unfortunately, it was impossible for the study members of the psychiatric studies to trace back a copy of the Amharic version of SF-36 used. We attempted to contact the authors of the HIV study above on four occasions to obtain their Amharic version of SF-36 but received no reply. The developers of SF-36 did not hold an Amharic version.

4.5 DEVELOPING THE AMHARIC SF-36 HRQOL FOR OUR STUDY IN ETHIOPIA

In 2002, the Scientific Advisory Committee of the Medical Outcomes Trust published recommendations including that focus groups and interviews with patients be conducted before developing a HRQoL tool, so that its content is grounded in the conceptualization of HRQoL impacts from the patient's perspective (Aaronson *et al.*, 1992). Such focus groups should purposely include representatives from both genders and a broad range of cultural groups, age groups and impairments.

Instrument translation and adaptation

We started by translating the English SF-36v2 in Amharic. Amharic is one of the official language of Ethiopia; it is commonly used in the capital city, and is the working language at ALERT hospital. The questionnaire was first translated by two native Amharic speakers fluent in English. A team consisting of the translators, two doctors, a social worker and a nurse reviewed the translation. The review was based on two assumptions: that the translation should replicate the original as closely as possible in capturing the closest possible meaning for purposes of cross-cultural comparisons; and that the translation should also be sensitive to adaptation of the instrument to the local socio-economic and cultural setting. For example "pushing a vacuum cleaner, bowling, or playing golf" were removed, leaving only "moving a table" as an example for moderate activity. The two previous reports on the use of Amharic SF-36 mentioned that "climbing stairs" was replaced by "walking up a hill" in their translation, but the group in Addis felt comfortable using "climbing stairs" and adding "walking up a hill" as a second option. Distance in miles and yards were changed to kilometres and metres which are more commonly used in Ethiopia. The

agreed-on translation was then discussed in a focus group with two doctors, two nurses, an occupational therapist and seven patients of various ages and leprosy experience (i.e. two newly diagnosed patients, three patients in reaction and two old patients coming for ulcer management). After some minor adjustment in language expressions, a final version was chosen and back translated into English by an independent translator. The new English translation was then reviewed against the original SF-36 for conceptual equivalence.

The above steps followed the standard procedures set by the original developers of SF-36 when translating SF-36 into another language (Ware, 1993):

1. Translator(s) is briefed on socio-demographic characteristics of target population, mode of administration of the survey instrument, and where the survey will be administered;
2. Provide translator with specific instructions about the reading level he/she should be aiming for in the translation and whether he/she should use language that is going to be widely understood by a variety of speakers of the target language or whether the translation should reflect language usage by speakers from a particular region or country;
3. Translator(s) reviews original language survey instrument before translation to identify items, terms or concepts that are difficult to translate;
4. Translator(s) meets with survey user to discuss problem items, terms or concepts and to obtain additional clarification or information on goal or intent of the English language item, term or concept;
5. Translation into target-language by a professional translator who is a native speaker of the target language (preferably a certified translator);
6. Back-translation from target-language into English by professional or certified translators;
7. Review of translation by bilingual reviewers (or other professional translators);
8. Review of original English-language instrument and back-translation;
9. Resolve discrepancies or problems in the translation by a committee that includes the translator, back-translator and reviewers (this may require one or more phone or in-person meetings).

Our version of the Amharic SF-36 is in Appendix 9.

Validity and reliability of Amharic SF-36 in leprosy patients

A HRQoL measurement needs to be reliable and valid. Validity is the degree to which the measure reflects what it is supposed to measure rather than something else. To infer validity the following kinds of evidence are generally used: content validity, criterion validity, construct validity and responsiveness to change. This is all work done during the development of SF-36 as an international HRQoL measurement tool. Validation of a translated questionnaire can be done by comparing its reliability and validity with a validated QOL tool in that language. Previous comparisons between SF-36 and WHOQOL-BREF have been successfully done in patients with HIV, showing that there are good correlations between the corresponding domains/scales of the two instruments (Hsiung *et al.,* 2005). Validation of the Amharic SF-36 in our study was done by comparison with an already validated Amharic WHOQOL-BREF (Araya *et al.,* 2007, 2011). A minimum sample size of 30 was advised by the study statistician, after review of published literature. Another measure of validity for SF-36 in leprosy patients was to assess known-group validity by comparing SF-36 scores with symptom frequency and symptom severity in leprosy patients.

Reliability refers to the extent to which a measure yields the same number or score each time it administered, all other things being equal (i.e. true change has not occurred in the attribute being measured). Inter-rater reliability for workers using the scale is required as a preliminary to any new research. A high proportion of leprosy patients are illiterate (42% in our group) and the assessment on QOL was done by an interviewer. It is essential to demonstrate that interviewers are collecting reliable data. This required a separate exercise in which paired blinded assessments were collected from a series of typical subjects/patients, and an inter-item correlation test was carried out. Again a minimum sample size of 30 was advised by the study statistician, after review of published literature.

Internal consistency reliability was determined by measuring Cronbach's α.

We hypothesized that if both instruments captured the health-related QOL of leprosy patients, then:

1. The corresponding domain/scale of both instruments should be positively correlated, i.e. the physical, psychological, and social domains of the WHOQOL-BREF should be significantly correlated with PF, MH and SF scales of the SF-36 respectively;
2. The physical and psychological domains of the WHOQOL-BREF should have weak associations with MCS and PCS of the SF-36, respectively;
3. The domain/scale score of both instruments should be positively correlated with self-perceived health status (question 2 in both instruments);
4. The domain/scale score of both instruments should be inversely correlated with the number and intensity of leprosy related symptoms.

Methods

One hundred patients with leprosy attending the leprosy clinic at ALERT hospital were interviewed for this study, over a period of 15 days. Half of this group (n=50), Group A, were interviewed by the same interviewer, on the same day with two different questionnaires: Amharic WHOQOL-BREF and Amharic SF-36. The other half (n=50), Group B, were interviewed by two different interviewers, on the same day with the same instrument, Amharic SF-36. The two interviewers were blinded from each other's interview results. The interviewers were a pool of three members of staff: two nurses and a social worker, who had previously received training in questionnaire administration and taken part in some of the translation exercise. All of the participants were interviewed; none of them self-completed the questionnaires. A specifically designed form was also completed to collect demographic data, disease status and symptomatology (Appendix 10).

Statistical analysis

Reverse score items were adjusted in SF-36 for questions SF02, GH02, GH04, VT03, VT04, MH01, MH02, MH04 and in WHOQOL-BREF for questions 3, 4 and 26. The scoring system recommended by the tool developers were followed for both the WHOQOL-BREF (WHO, 2012c) and the SF-36 (Ware, 1993).

Data were then analysed in the following aspects:

1. Descriptive statistics;

2. Tests of scaling assumptions (multi-trait scaling methods);
3. Reliability (Cronbach's α for internal consistency reliability);
4. Convergent and discriminant validity (correlations between scores of the two instruments);
5. Known-groups validity (correlations between scores and symptoms);
6. Inter-rater reliability (correlation between two interviewers per domain/ scale and global score);
7. Validity of Amharic SF-36.

Data was computed using SPSS for Windows, version 20.

Results

Baseline Characteristics

The characteristics of the 100 participants are summarized in Table 4.1.

There was a 1:3 ratio of female to males in the group of 100 patients interviewed. Although only 2% had received tertiary education, a total of 58% had been to school and were literate. Despite ALERT hospital being an urban centre, 27% of patients interviewed were rural residents. Most patients (81%) attending the clinic were being treated for a reaction and were on steroids; only 31% were acutely unwell on the day of the interview. A total of 41% were on MDT.

Disability grading was done by looking at the Eye Hand Foot score recommended by the WHO. A total maximum score of 12 is possible, reflecting disability in each of the six body parts. The obtained scores were categorized into "0= No disability" (24%), "1-4= Moderate disability" (55%) and "5-12= Severe disability" (21%). A high percentage (79%) of patients reported experiencing more than four leprosy related symptoms, with 46% of patients scoring higher than the mean in terms of severity.

Characteristics of patient group		**Total group n= 100 (%)**	**Group A: WHOQOL-BREF vs.SF-36 comparison group**	**Group B: SF-36 inter–rater reliability group**
Number of patients		**100**	**50**	**50**
Age (years) Median		**35**	**33.5**	**37.4**
Female: male ratio		**1:3**	**2:3**	**1:2**
Education level	**None** **Primary** **Secondary** **Tertiary**	**42%** **30%** **26%** **2%**	**17 (34%)** **17 (34%)** **15 (30%)** **1 (2%)**	**25 (50%** **13 (26%)** **11 (22%)** **1 (2%**
Literacy	**No** **Yes**	**42%** **58%**	**18 (36%)** **32 (64%)**	**24 (48%)** **26 (52%)**
Lives:	**Alone** **With others**	**16%** **84%**	**5 (10%)** **45 (90%)**	**11 (22%)** **39 (78%)**
Residence: Rural/Urban	**Rural** **Urban**	**27%** **73%**	**10 (20%)** **40 (80%)**	**17 (34%)** **33 (66%)**
Duration of leprosy symptoms (years: mean range)		**2.9 (0-14)**	**3 (0-10)**	**3 (0-10)**
On MDT		**41%**	**22 (44%)**	**19 (38%)**
On Steroids for reactions		**81%**	**42 (94%)**	**39 (78%)**
Type of Reaction	**ENL** **T1R**	**20%** **61%**	**9 (18%)** **33 (66%)**	**11 (22%)** **28 (56%)**
Health status at today's attendance	**Sick** **Stable**	**31 %** **69 %**	**19 (38%)** **31 (62%)**	**12 (24%)** **38 (76%)**
Hospital admission	**Never** **Past** **Presently**	**66%** **27%** **7%**	**33 (66%)** **14 (28%)** **3 (6%)**	**33 (66%)** **13 (26%)** **4 (8%)**
Disability grading (Total EHF score)	**None =0,** **Moderate= 1-4** **Severe = 5-12**	**24%** **55%** **21%**	**15 (30%)** **18 (36%)** **17 (34%)**	**9 (18%)** **37 (74%)** **4 (8%)**
Number of positive symptoms:	**None** **1-3 symptoms** **4-7 symptoms**	**5 %** **16%** **79%**	**5 (10%)** **9 (18%)** **36 (72%)**	**0 (0%)** **7 (14%)** **43 (86%)**
Severity of symptoms:	**None** **Moderate** (lower than group mean) **Severe** (higher than group mean)	**4%** **50%** **46%**	**4** **23 (46%)** **23 (46%)**	**0** **27 (54%)** **23 (46%)**
Self-perceived health status (GH1 from SF-36):	**Poor** **Fair** **Good** **Very Good** **Excellent**	**7%,** **40%,** **33%,** **16%** **4%**	**3 (6%),** **20 (40%),** **15 (30%),** **8 (16%)** **4 (8%)**	**4 (8%),** **20 (40%)** **(36%)** **8 (16%)** **0**

Table 4.1 Characteristics of 100 patients with leprosy enrolled QoL this study

Descriptive statistics for the WHOQOL-BREF vs SF-36 comparison

Each of the 50 Group A patients interviewed had their scores analysed by domains for both questionnaires and the score distribution is shown in Table 4.2.

The physical and environmental domains of WHOQOL-BREF and six out of the 8 scales of the SF-36 were positively skewed, indicating distributions with more patients scoring lower than average health related quality of life.

	Number of items	Mean	Standard Deviation	Minimum	Percentile 25	Median	Percentile 75	Maximum	Percent scoring at the floor	Percent scoring at the ceiling
WHOQOL-BREF										
PHYS	7	51.2	16.0	10.7	39.3	50.0	64.3	75.0	2.00%	8.00%
PSYCH	6	53.7	16.4	12.5	41.7	58.3	66.7	80.0	2.00%	2.00%
SOCIAL	3	46.1	22.6	0.0	33.3	50.0	66.7	75.0	8.00%	16.00%
ENVIR	8	40.9	14.9	12.5	31.3	40.6	50.0	71.9	2.00%	2.00%
SF-36										
PF	10	71.5	33.9	0.0	50.0	90.0	100.0	100.0	6.00%	34.00%
RP	4	61.5	29.1	0.0	43.8	50.0	93.8	100.0	4.00%	24.00%
BP	2	50.9	30.3	0.0	32.0	42.0	74.0	100.0	8.00%	18.00%
GH	5	50.0	24.8	5.0	27.0	45.0	67.0	100.0	2.00%	4.00%
VT	4	55.0	22.5	12.5	50.0	50.0	75.0	100.0	2.00%	6.00%
SF	2	48.0	33.9	0.0	25.0	50.0	62.5	100.0	16.00%	20.00%
RE	3	60.2	28.6	0.0	50.0	50.0	75.0	100.0	4.00%	22.00%
MH	5	52.4	21.8	0.0	45.0	50.0	60.0	100.0	2.00%	4.00%
PCS		46.4	10.3	27.9	37.4	46.1	56.8	62.0	2.00%	2.00%
MCS		38.7	10.9	15.4	32.3	38.4	43.9	62.8	2.00%	2.00%

Phy- physical domain, Psy- psychological domain, Soc- social domain, Env- environment domain, PF- physical functioning, RP- role physical, BP- bodily pain, GH- general health perceptions, VT- vitality, SF- social functioning, RE- role emotional, MH- mental health, PCS- physical component summary, MCS- mental component summary

Table 4.2 Table Score distribution of the WHOQOL-BREF and SF-36 (n=50)

All four domains of the WHOQOL-BREF had trivial floor and ceiling effects. Ceiling effect is measured by the proportion of people getting the highest possible score, whilst floor effects reflect the proportion of people receiving the lowest possible score. The highest ceiling effect was noted in the physical functioning (PF) scale of SF-36 (34%) indicating that one third of patients were able to perform physical activities without limitations. Noteworthy ceiling effects were observed for the role-disability scales (24% for role physical (RP) and 22% for role emotional (RE)) in the SF-36, indicating that almost one quarter of patients with leprosy did not

feel that their physical health or emotional problems resulted in difficulties with work or other activities. A modest ceiling effect was observed for social functioning (SF) with 20% of patients able to perform social activities without interference.

Test of scaling assumption for the WHOQOL-BREF vs SF-36 comparison

To evaluate item internal consistency test and item discriminant validity test for both instruments, multi-trait scaling techniques were used (Table 4.3). Item internal consistency describes to what extent items belonging to the same scale do correlate one with each other and item discriminant validity shows that items belonging to different scales should not correlate to a great extent.

	Range of Correlations		Internal Consistency Tests[c]		Discriminant Validity Test [d]	
	Item-internal consistency [a]	Item-discriminant validity [b]	#Success/ total	Success rate (%)	#Success /total	Success rate (%)
WHOQOL-BREF (n=50)						
Phy	0.4-0.84	0.01-0.78	7/7	100%	27/28	96%
Psy	0.53-0.80	0.06-0.78	6/6	100%	24/24	100%
Soc	0.70-0.81	0.27-0.53	3/3	100%	12/12	100%
Env	0.46-0.71	0.27-0.74	8/8	100%	30/32	100%
SF-36 (n=100)						
PF	0.64-0.97	0.25-0.78	10/10	100%	78/80	97.5%
RP	0.82-0.94	0.31-0.89	4/4	100%	32/32	100%
BP	0.79-0.79	0.45-0.74	2/2	100%	16/16	100%
GH	0.65-0.80	0.27-0.59	5/5	100%	39/40	97.5%
VT	0.49-0.73	0.14-0.66	4/4	100%	32/32	100%
SF	0.88-0.88	0.29-0.63	2/2	100%	16/16	100%
RE	0.93-0.97	0.45-0.85	3/3	100%	24/24	100%
MH	0.61-0.8	0.27-0.61	5/5	100%	40/40	100%

[a]Correlation between items and hypothesized scale corrected for overlap
[b]Correlation between items and other scales
[c]Number ≥ 0.40
[d]Number of correlations significantly higher/total number of correlations

Table 4.3 Tests of item internal consistency and discriminant validity of the WHOQOL-BREF and SF-36

The range of the item internal consistency for the WHOQOL-BREF was 0.4-0.84 and 0.49-0.97 for SF-36. A perfect success rate, with the criteria of correlations, which equal or exceed 0.40, was observed in the tests of the item internal consistency for both instruments. Results of item discriminant validity and scaling success rates

are also shown, with a near perfect success rate achieved in tests of the item discriminant validity for both instruments.

Reliability

Table 4.4 shows internal consistency for reliability tested by Cronbach's α. The Cronbach's α values for internal consistency (reliability) for all the SF-36 scales were above 0.70 showing good internal reliability of SF-36. The physical, psychological and environmental domains of WHOQOL-BREF also had Cronbach's α values above 0.70. The social domain had a lower Cronbach's α than expected at 0.652. Looking back into the three questions being assessed, it was noted that question 21 dealt with sexual function asking: "How satisfied are you with your sex life?" In the Ethiopian context, discussing your sex life is still fairly taboo and it was theorized that this item was negatively influencing the internal reliability of the social domain. Re-running the analysis by omitting question 21, greatly improved the Cronbach's α from 0.652 to 0.851 **(**Table 4.5).

QoL questionnaire	Domains	Cronbach's α	N of Items
WHOQOL-BREF	Phy	.768	7
	Psy	.738	6
	Soc	.652	3
	Envir	.744	8
SF-36	PF	.968	10
	RP	.966	4
	BP	.923	2
	GH	.877	5
	VT	.817	4
	SF	.928	2
	RE	.975	3
	MH	.894	4

Table 4.4 Reliability statistics for WHOQOL-BREF and SF-36

	Cronbach's α	Cronbach's α Based on Standardized Items	N of Items
Qu 20, 21 and 22	.652	.685	3
Qu 20 and 22 only	.851	.854	2

Table 4.5 Reliability statistics for WHOQOL social domain

Convergent and discriminant validity

The correlations for inter-domain/scale of the WHOQOL-BREF and the SF-36 are presented in Table 4.6.

The range of correlations for inter-domain/scales of the WHOQOL-BREF is 0.46-0.76 (all p<0.001), showing a range of moderate (30%) to high (60%) associations among domains. All the inter-scale correlations of the SF-36 showed moderate (14%) to high (76%) associations (*r* range 0.38-0.89, all p<0.001).

	WHOQOL-BREF						SF-36							
Name	**Q1**	**GH1**	**PHY**	**PSY**	**SOC**	**ENV**	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**
Q1	1.00													
GH1	0.41**	1.00												
PHY	0.69**	0.43**	1.00											
PSY	0.56**	0.32*	0.76**	1.00										
SOC	0.21	0.27	0.46**	0.48**	1.00									
ENV	0.48**	0.25	0.64**	0.68**	0.50**	1.00								
PF	0.23	0.46**	0.33*	0.32*	0.25	0.20	1.00							
RP	0.34*	0.59**	0.46**	0.35*	0.17	0.30*	0.58**	1.00						
BP	0.36*	0.76**	0.47**	0.35*	0.16	0.21	0.54**	0.70**	1.00					
GH	0.25	0.78**	0.28	0.26	0.10	0.19	0.41**	0.60**	0.75**	1.00				
VT	0.33*	0.70**	0.42**	0.39**	0.05	0.23	0.38**	0.55**	0.66**	0.70**	1.00			
SF	0.16	0.68**	0.38**	0.25	0.15	0.37*	0.39**	0.57**	0.72**	0.59**	0.55**	1.00		
RE	0.44**	0.52**	0.62**	0.50**	0.19	0.30*	0.64*	0.74**	0.71**	0.50**	0.54**	0.57**	1.00	
MH	0.51**	0.67**	0.60**	0.46**	0.08	0.34*	0.46**	0.47**	0.73**	0.62**	0.63**	0.60**	0.65**	1.00
PCS	0.23	0.67**	0.32*	0.29*	0.22	0.20	0.81**	0.83**	0.80**	0.76**	0.59**	0.59**	0.65**	0.49**
MCS	0.45**	0.70**	0.61**	0.47**	0.06	0.35*	0.35*	0.54**	0.75**	0.63**	0.75**	0.77**	0.77**	0.89**

**. Correlation is significant at the 0.001 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Q1-overall QOL in WHOQOL-BREF, GH1-general health in WHOQOL-BREF, Phy-physical domain, Psy- psychological domain, Soc-social domain, Env-environment domain, PF-physical functioning, RP-role physical, BP-bodily pain, GH-general health perceptions, VT-vitality, SF-social functioning, RE-role emotional, MH-mental health, PCS-physical component summary, MCS-mental component summary

In analysing level of correlation, the following have been assumed: High correlation: 0.5 to 1.0 or -0.5 to 1.0; *Moderate correlation:* 0.3 to 0.5 or -0.3 to 0.5; *Low correlation*: 0.1 to 0.3 or -0.1 to -0.3

Table 4.6 Pearson's Correlation Coefficients between WHOQOL-BREF and SF-36 *(n=50)*

Within WHOQOL-BREF, the range of correlation between the general QoL question (Q1) and the domains was from 0.21-0.69, whilst between the general health question (GH1) and the domains it was 0.25-0.43. The weak correlations were between the social domain and general QoL and health questions (r=0.21 and r=0.27 respectively) and the environmental domain and the general health question (r=0.25).

Within SF-36, there was good correlation between the general health question (GH) and all the scale (r range 0.47-0.76).

Correlation between scores of the WHOQOL-BREF and the SF-36 are also shown in this table. The relationship of the general item, Q1 (overall QoL from WHOQOL-BREF) showed weak to moderate associations with scales of SF-36, including with the general health question GH (r=0.41, p<0.001). The highest association (r=0.51) was between Q1 and MH of the SF-36. This implies that both measured similar concepts. Question GH from SF-36 showed weak to moderate associations with WHOQOL-BREF domains but a high association (r=0.78) with GH1 implying that both measured similar concepts, and that patients were responding to this question consistently with both questionnaires. The hypothesis that domain/scale scores should be positively correlated to self-perceived health status is better supported with the SF-36 in this group of patients.

Looking in more detail at the associations between the SF-36 scales and the WHOQOL-BREF domains, weak associations occurred between the social domain of WHOQOL-BREF and all SF-36 scale items (r range 0.05 -0.25), as well as between the environmental domain of WHOQOL-BREF and scale items PF, BP, GH, and VT of the SF-36 (r range 0.19-0.23). Moderate associations were seen between the physical domain of WHOQOL-BREF and PF, RP, BP, GH and VT of SF-36 (r range 0.28 and 0.47); and the psychological domain of WHOQOL-BREF and PF, BP, RP, VT and MH of SF-36 (r range 0.32- 0.46). The highest correlations were found between the physical domains of WHOQOL-BREF and RE (r=0.62) and MH (r=0.60) of the SF-36.

The correlation between the physical and psychological domains of the WHOQOL-BREF and PF and MH of the SF-36 were 0.33 and 0.46 respectively, but the association between the social domain and SF scale was low (r=0.15). The first hypothesis that the corresponding domain/scale of both instruments should be positively correlated is partially supported.

Regarding the summary measures of the SF-36, the physical domain of the WHOQOL-BREF has weak association with PCS (0.32) and the psychological domain of WHOQOL-BREF has strong association with MCS (r=0.47). A weak associations was found between the psychological domains of the WHOQOL-BREF

and PCS of SF-36 (r=0.29). This supports the hypothesis that the psychological domain of WHOQOL-BREF should have weak association with PCS, but the correlation between the physical domain and MCS was found to be strong (r=0.61).

Within SF-36, the strongest association were between PCS and PF, RP, BP and GH (0.75-0.83) and between MCS and BP, VT, SF, RE and MH (0.76-0.89). Previous studies have found that, three scales (PF, RP, BP) correlated most highly with the physical component (PCS) measure whilst the mental component (MCS) correlated most highly with the MH, RE, and SF scales (Gandek *et al.*, 1998a; Ware, 1993; McHorney *et al.*, 1993).

Overall, the results of validity examination showed that SF-36 has better convergent and discriminant validity than WHOQOL-BREF in this group of patients. The social domain of WHOQOL-BREF showed particularly poor correlation, which might be related to the small number of questions in this domain or to poor internal validity of this domain (Cronbach's α= 0.652).

Known group validity

Table 4.7 shows that, in general, leprosy patients with a greater number of symptoms scored significantly lower on the physical domain of WHOQOL-BREF and in three scales of SF-36 (RP,BP, MH) and MCS (all $p<0.05$). Patients with less severe symptoms scored significantly higher scores on physical, psychological and environmental domains as well almost all the scales of SF-36. This supports the fourth hypothesis and indicated good known-groups validity of both instruments.

		WHOQOL-BREF				SF-36									
		PHYS	PSYCH	SOC-IAL	ENVIR	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Severity Level	None	67.9	68.8	41.7	52.3	76.3	87.5	83.0	69.3	73.4	62.5	87.5	80.0	51.7	51.4
	Low	55.5	56.6	54.3	44.9	75.7	69.6	61.5	56.8	57.1	60.3	63.0	55.2	49.7	40.3
	High	43.7	48.0	38.3	34.6	66.5	48.9	34.7	39.9	49.7	33.2	52.5	44.8	42.2	34.9
p value		<0.001	<0.001		<0.001		<0.001	<0.001	<0.001		<0.05	<0.05	<0.05	<0.05	<0.05
Number of symptoms	None	67.9	68.8	41.7	52.3	76.3	87.5	83.0	69.3	73.4	62.5	87.5	80.0	51.7	51.4
	1-3	56.4	52.9	42.5	40.9	83.0	75.6	57.7	59.4	63.8	63.8	68.3	64.0	50.1	43.9
	4-7	47.8	52.2	47.6	39.5	67.8	54.7	45.4	45.3	50.5	42.0	54.9	46.1	44.8	35.9
p value		<0.05					<0.001	<0.05					<0.001		<0.001

Table 4.7 Comparison of the mean scores in different domains of WHOQOL-BREF and SF-36 for leprosy patients with different symptoms severity

Inter-rater reliability

One way of performing reliability testing is to use the intra-class correlation coefficient (ICC). It can be defined as, "the proportion of variance of an observation due to between-subject variability in the true scores". The range of the ICC may be between 0.0 and 1.0. The ICC will be high when there is little variation between the scores given to each item by the raters, e.g. if all raters give the same, or similar scores to each of the items. The ICC is an improvement over Pearson's r and Spearman's ρ, as it takes into account of the differences in ratings for individual segments, along with the correlation between raters (Shrout & Fleiss, 1979).

In this study intra-class correlation was calculated by using ICC (2), "Two-Way Random" method which works on two assumptions: 1) it models both an effect of rater and of ratee (i.e. two effects) and 2) assumes both are drawn randomly from larger populations (i.e. a random effects model). Mean rating was selected, computing first the mean of each of the 8 domains of SF-36 (PF, RP, BP, GH, VT, SF, RE, MH), for each of the Group B 50 participants in both sets of interviews. The measure of consistency was chosen as this is recommended when comparing means and results are summarized in Table 4.8.

SF-36 domain	Intra-class Correlation[a] Average Measures	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Significance
PF	.830	.700	.903	5.873	49	49	.000
RP	.737	.537	.851	3.804	49	49	.000
BP	.809	.664	.892	5.239	49	49	.000
GH	.987	.977	.993	76.179	49	49	.000
VT	.988	.978	.993	81.584	49	49	.000
SF	.976	.957	.986	41.101	49	49	.000
RE	.805	.657	.890	5.140	49	49	.000
MH	.934	.884	.963	15.178	49	49	.000

Two-way random effects model where both people effects and measures effects are random.

a. Type C intra-class correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.

Table 4.8 Intra-class Correlation Coefficient

An intra-class correlation of 0.7 is deemed acceptable, above 0.8 is optimal and a score of above 0.9 would be considered excellent inter-rater reliability. Our results show that for four out of the eight domains of SF-36 inter-rater reliability was excellent, three were in the optimal range and one, social functioning was in the acceptable range. The p-values, all under 0.001, were statistically significant.

Conclusion

The findings of the validity and reliability tests for the Amharic SF-36 are summarized here.

As the questionnaire were filled in by trained interviewers there were only a couple of missing answers. Tests of scaling assumption showed that the Amharic SF-36 had high item internal consistency and item discriminant validity. We found positively skewed score distributions of the WHOQOL-BREF domains and SF-36 scales indicating more patients scored less than the mean group QOL score. But since 69 % of patients interviewed were attending hospital because they were unwell, this result would be expected, and confirms validity. This was further supported by the high ceiling effect noted in the PF scale of SF-36 (34%) and 24% for RP and 25% for RE, supporting the theory that of our patient group a large proportion would have some limitations in physical functioning, and work/social activities.

Internal consistency reliability was very good in both WHOQOL domains and SF-36 scales. The Cronbach's α values for most domain/scale items exceeded 0.70, but results were in a higher range for the SF-36 (0.82-0.97) than for the WHOQOL-BREF (0.65-0.77), suggesting that the Amharic SF-36 may have better reliability than the Amharic WHOQOL-BREF in this group of patients. The social domain of WHOQOL-BREF was the only item with a Cronbach's α lower than 0.70.

Overall, validity examination showed that convergent and discriminant validity for SF-36 inter-scale was better than that for WHOQOL-BREF inter-domain, in this group of patients. Correlations between the scores of corresponding domains/scales between the WHOQOL-BREF and SF-36 supported the first hypothesis that the corresponding domain/scale of both instruments should be positively correlated with the exception that the association between the social domain and SF scale was low (r=0.15). The second hypothesis stating that the physical and psychological domains

of the WHOQOL-BREF should have weak associations with MCS and PCS of the SF-36, respectively was only partially supported as the correlation between the physical domain and MCS was found to be strong (r=0.61), possibly reflecting the strong mental health component of the WHOQOL-BREF. The third hypothesis that domain/scale scores should be positively correlated to self-perceived health status is better supported with the SF-36 in this group of patients. Good known-group validity for both instruments supported the fourth hypothesis as there was a consistent trend of decreasing scores in the WHOQOL-BREF and SF-36 with increasing severity and number of leprosy related symptoms.

Inter-rater reliability for the SF-36 was very good with all the scales scoring between the acceptable and excellent range.

This study showed that the Amharic translations of both the WHOQOL-BREF and the SF-36 had good reliability and validity amongst leprosy patients, with the SF36 also showing good inter-rater reliability.

4.6 AMHARIC SF-36 IN LEPROSY PATIENTS

The Amharic SF-36 was administered to 100 patients with leprosy presenting at the clinic during the questionnaire validation exercise. We looked at the quality of life in these patients comparing their mean scores with those found in another study in which the Amharic SF-36 was validated in the Ethiopian general population (Kebede *et al.*, 2004). This study was done in 1990 respondents, 90% of which were rural dwellers. For our 100 leprosy patients, whose baseline characteristics are described Table 4.9, the mean scores in the eight scales and the two summary score of SF-36 compared to those of the general population norms study done in Ethiopia are shown in Figure 4.2.

Characteristics of patient group	Total group n= 100 (%)
Age (years) Median	35
Female: male ratio	1:3
Education level: N (none) **P (primary)** **S (secondary)** **T (tertiary)**	N: 42% P: 30% S: 26% T: 2%
Literate	No: 42% Yes: 58%
Lives: Alone/ with others	Alone: 16% Others: 84%
Residence	Rural: 27% Urban: 73%
Length of leprosy symptoms (in years: mean, range)	2.9 (0-14)
On MDT	41%
On Steroids for reactions	81%
Type of Reaction	ENL: 20% T1R: 61%
Health status at today's attendance	Sick: 31 % Stable: 69 %
Hospital admission	Never: 66% Past: 27% Presently: 7%
Disability grading (Total EHF score): None =0 **Moderate= 1-4** **Severe = 5-12**	None: 24% Mod: 55% Severe: 21%
Number of positive symptoms	None: 5 % 1-3 Sx: 16% 4-7 Sx: 79%
Severity of symptoms: **None, Moderate (lower than group mean),** **Severe (higher than group mean)**	None: 4% Mod: 50% Severe: 46%
Self-perceived health status (GH1 from SF36):	Poor: 7%, Fair: 40%, Good: 33%, Very Good: 16%, Excellent: 4%

Table 4.9 Baseline characteristics of leprosy patients attending clinic (n=100)

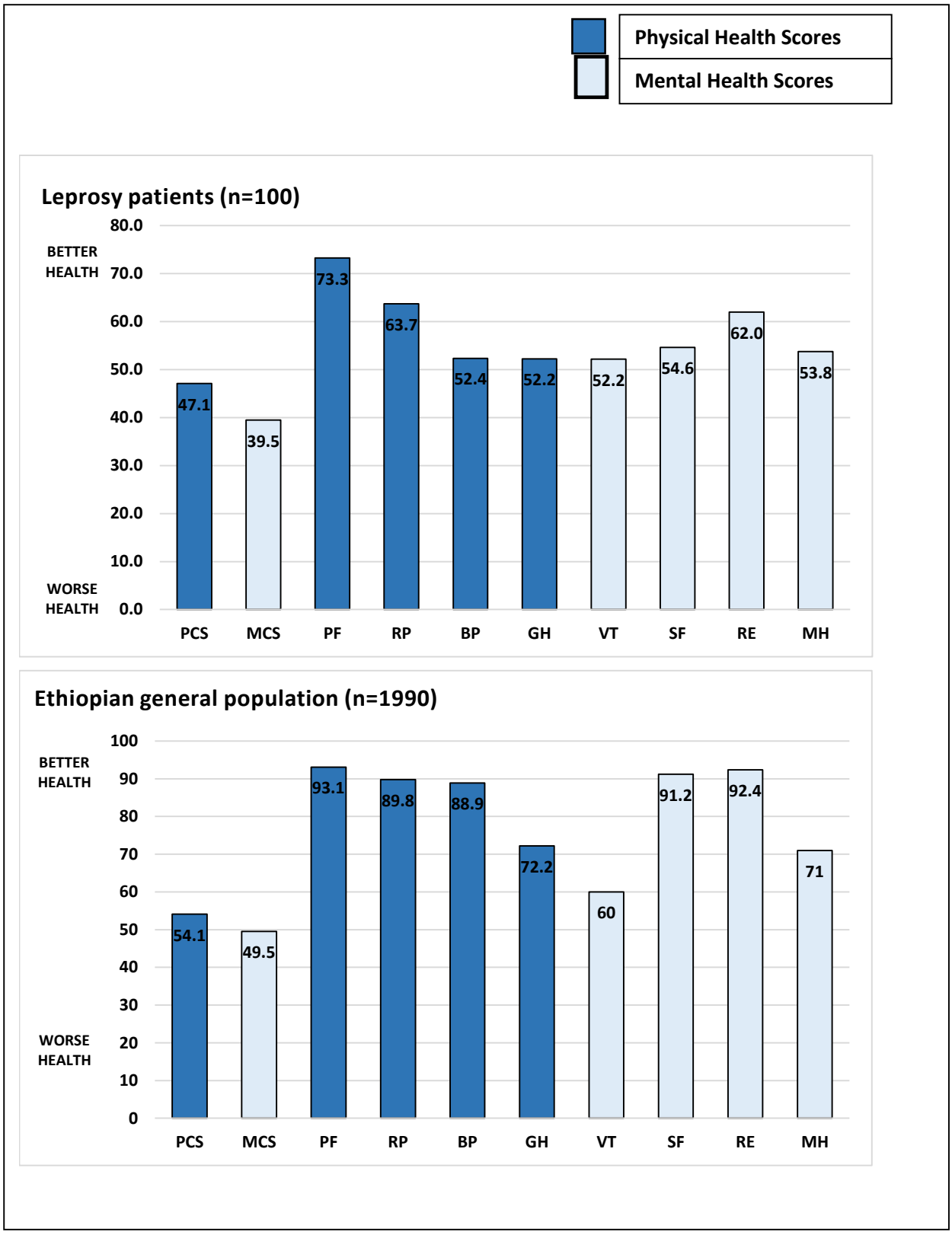


Figure 4.2 Mean scores for leprosy patients compared to Ethiopian population norms

The SF-36 scores for the eight scales and the two summary components were lower for the leprosy patients compared to the general population norms (Figure 4.2). The differences between scores were more marked in the scales for bodily pain (36.6 points) and social functioning (36.6 points), followed by emotional role (30.4 points), and physical role (26.1 points). General health and physical functioning scored 20 points less in the leprosy patients and mental health 17.3 points less. Vitality was the least affected scale with a score difference of only 7.8 points. The two summary components showed a difference of 10 points in MCS and 7 point in PCS between patients with leprosy and the general population.

Table 4.10 shows the mean score breakdown by patient categories with statistically significant differences marked. Women scored higher than men across all summary scales except in the general health domains. Younger patients generally had better scores than older patients and quality of life scores improved in all the scales with increasing education. None of these findings were found to be statistically significant.

Literate patients had better scores in all the scales and significant differences were noted in physical functioning, emotional role, mental health and the two component scores. Single patients scored generally more than married or widowed patients but patients living alone scored less than those living with family members. Significant differences were seen between those who reside in rural areas and urban areas, with lower scores in the scales BP, GH, SF, MH, PCS and MCS for rural residents.

The longer patients had had symptoms of leprosy the higher they scored across all the scales; patients scored better when not on MDT or steroids. Among these results the only significant finding was that patients on MDT had lower social functioning.

The higher the grade of disability as assessed by the EHF score, the lower the scores across all scales of SF-36, but in particular in PF, BP, SF, RE, MH, PCS, and MCS (all $p>0.05$). The differences between quality of life score and level of severity of symptoms were all statistically significant as scores decreased in all scales with increasing severity. This was also true for the number of symptoms experienced. Patients who felt sick on the day of the questionnaire administration scored significantly less in all scores except RE and MCS.

		PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Sex	Female	75.3	69.8	57.1	50.8	53.5	61.5	69.7	53.3	48.1	41.0
	Male	72.1	60.3	49.7	53.0	51.5	50.8	57.7	54.0	46.5	38.6
Age category	Older	67.9	61.6	49.5	50.2	51.2	56.1	57.4	51.1	46.0	38.7
	Younger	78.0	65.6	54.8	54.1	53.1	53.3	66.0	56.1	48.0	40.2
Education level	None	65.0	59.2	46.4	46.9	49.6	46.7	55.0	48.8	44.9	37.0
	Primary	79.6	65.0	55.6	54.2	56.7	60.8	64.2	57.8	48.3	41.3
	Secondary	78.7	69.0	57.8	58.1	51.3	59.8	70.2	56.8	49.0	41.2
Literate	No	62.8*	57.4	45.0	46.2	49.3	46.7	53.2*	47.7*	44.3*	36.7*
	Yes	80.8*	68.2	57.7	56.6	54.3	60.3	68.4*	58.1*	49.1*	41.5*
Marital Status	Single	77.2	69.3	56.1	56.7	56.8	56.4	70.7	57.0	48.4	41.8
	Married	76.0	63.1	49.8	51.3	49.4	51.8	58.3	53.5	47.3	38.0
	Widowed	57.6	54.4	52.5	46.2	51.5	59.6	55.9	48.2	43.8	39.3
Lives with	Alone	76.9	60.9	51.4	48.5	55.1	49.2	56.3	50.3	47.7	37.2
	Others	72.6	64.2	52.5	52.9	51.6	55.7	63.1	54.4	47.0	39.9
Residence	Rural	62.3	55.3	39.5*	42.1*	45.1	39.4*	51.5	44.3*	43.3*	34.7*
	Urban	77.3	66.8	57.1*	56.0*	54.8	60.3*	65.9	57.3*	48.5*	41.3*
Duration of leprosy	0-5 years	70.0	60.8	51.3	50.7	50.8	53.0	59.8	53.7	46.1	39.2
	6+ years	84.7	73.9	56.0	57.6	57.1	60.2	69.7	53.9	50.8	40.4
On MDT	No	72.3	66.5	54.7	58.5	51.8	69.2*	65.2	57.7	47.6	42.4
	Yes	73.6	62.6	51.4	49.8	52.3	49.0*	60.8	52.2	46.9	38.4
On steroid	No	77.5	64.0	54.9	48.7	50.6	44.6	59.9	54.0	47.9	37.5
	Yes	72.1	63.6	51.7	53.2	52.6	57.3	62.6	53.7	46.9	40.0
EHF score out of 12	None (0)	91.7*	74.2	62.5*	56.3	55.7	54.2	74.7*	61.3*	51.4*	41.5*
	Moderate (1-4)	67.7*	59.9	49.7*	50.1	50.8	54.5	58.2*	50.3*	45.8*	38.5*
	Severe (4-12)	66.7*	61.6	47.8*	53.0	51.8	55.4	57.5*	54.3*	45.6*	39.7*
Symptom Severity Level	None	76.3*	87.5*	83.0*	69.3*	73.4*	62.5*	87.5*	80.0*	51.7*	51.4*
	Low	82.0*	74.6*	62.0*	65.1*	59.8*	68.4*	70.8*	60.3*	51.2*	43.4*
	High	63.1*	49.2*	38.7*	36.2*	41.7*	38.3*	49.8*	44.0*	42.0*	34.1*
Number of symptoms	None	76.3	87.5*	83.0*	69.3*	73.4*	62.5	87.5	80.0*	51.7*	51.4*
	1-3	88.4	75.4*	67.0*	68.7*	66.4*	68.8	73.4	70.0*	52.2*	46.3*
	4-7	70.1	60.2*	47.9*	48.1*	48.3*	51.4	58.4	49.2*	45.8*	37.5*
Sick vs Stable	Sick	63.9*	51.4*	42.4*	42.8*	44.4*	44.0*	48.9*	51.0	42.9*	36.2
	Stable	77.4*	69.2*	56.8*	56.5*	55.7*	59.4*	67.9*	55.0	49.0*	41.0

**significant difference with p value >0.05*

Table 4.10 Mean SF-36 scores with socio-demographic and clinical correlates.

4.7 DISCUSSION

This study was assessing the reliability and validity of the Amharic translations of both the WHOQOL-BREF and the SF-36 in measuring quality of life in leprosy patients.

The Amharic translation of SF-36 was easy to use for the interviewers involved and it was generally felt that most patients understood the question being asked. Likert scales can be tricky for first time users and time was taken to give patients the chance to choose the nearest best-fit answer. The available Amharic version of WHOQOL-BREF obtained from Addis Ababa University was found to be well translated although there was a numbering error from question 15 onwards. Question 15 in the English version had been moved to question 25 in the Amharic version and question numbers 16 to 24 were amended so that the two translation matched exactly and score computation was correct.

Comparison between the Amharic SF-36, translated following standard procedures, and the validated Amharic WHOQOL-BREF found that item internal consistency and item discriminant validity were good. Internal consistency reliability estimates for each domain/scale exceeded 0.70, except for the social domain of WHOQOL-BREF where results were heavily skewed by Question 21 relating to satisfaction in sex life, a fairly taboo subject in Ethiopia. The strong correlation between all, except the social, WHOQOL-BREF domains with the mental component rather than the physical component may reflect the strong mental health component of the WHOQOL-BREF. Known-group validity for both instruments was demonstrated by the consistent trend of decreasing scores of the WHOQOL-BREF and SF-36 with increasing severity and number of leprosy related symptoms.

The inter-rater reliability was found to be very good. Intra-class correlation is rarely computed because different interviewers do not usually go back to ask respondents the same questions and groups of respondents interviewed by different interviewers are not always comparable. Especially in personal interview surveys, interviewers may be assigned to different areas of a city or region that differ a great deal compositionally. The participants' previous experience in this type of questionnaire might also be a factor that contributes to error. In our group of leprosy patients at ALERT being asked about quality of life was a novel concept and answers may have

been more thought out by the time the second interview occurred. It would have been interesting to keep a record of the interview order to test this theory.

The Amharic WHOQOL-BREF scores in our sample of 50 patients with leprosy where similar to those of a study in 120 Brazilian leprosy patients in reaction (Costa *et al.*, 2012). The mean scores for the physical domain were 51.2 for the Ethiopian patients and 48.2 for the Brazilian patients; mean psychological scores were 53.7 and 58.6 respectively; mean social domain scores were 46.1 and 61.7 respectively and finally in the environmental domain, the scores were 40.9 and 53. A large difference is noted in the social and environmental domains with Ethiopian patients scoring much lower, possibly reflecting poorer living conditions in this African setting. The results of quality of life study in relation to podoconiosis conducted in Ethiopia (Mousley *et al.*, 2013) allows us to compare domain scores (Table 4.11). Leprosy patients scored less that healthy controls in all domains. Results between patients with podoconiosis and leprosy were very close with leprosy patients scoring slightly more in the physical and psychological domains and slightly less in the social and environmental domains. The lower physical domain score in patients with podoconiosis may be explained by the physical limitation caused by the extreme leg swelling. Both diseases are highly stigmatising.

Variables/100 Mean	Podoconiosis cases (n=346)	Healthy controls (n=349)	Leprosy cases (n=50)
Physical Domain	47.89	68.12	51.2
Psychological Domain	51.12	66.98	53.7
Social Domain	52.12	67.16	46.4
Environmental Domain	43.06	56.44	40.04

Table 4.11 Comparison of Amharic WHOQOL-BREF domains scores between podoconiosis and leprosy cases and healthy controls in Ethiopia

The Indian study comparing WHOQOL-BREF score between 51 leprosy patients and 58 community members found that scores were significantly lower in the leprosy patients in the physical and psychological domains but not in the social relationship and environmental domain (Mankar *et al.*, 2011). The findings were similar in a Bangladeshi study (Tsutsumi *et al.*, 2007). A more recent study in Malawi used the

WHOQOL-BREF to compare quality of life between ex-leprosy patients living in leprosaria and those living in the community (Chingu *et al.*, 2013). In the last three studies mentioned the quality of life scores published for the WHOQOL-BREF where on a 0-20 score known as the raw score and the procedures taken to calculate the score were not clearly described making a direct numerical comparison of scores difficult. The WHOQOL-BREF developers suggest using a 0-100 score (WHO, 2012c). Findings of interest were that in patients with leprosy, those with higher grades of disability and lower education had significantly lower quality of life scores.

There are only two published studies assessing quality of life using SF-36 in leprosy in a clinical situation. Both studies were based in Brazil. One assessed the quality of life in 107 patients attending a health facility for leprosy treatment (Lustosa *et al.*, 2011) and the second quality of life in 49 patients on treatment for PB leprosy (Bottene & Reis, 2012). The second study found that quality of life scores in 63% of patients with PB leprosy was not affected. Most of these patients were diagnosed early with no leprosy reaction or nerve function impairment. The Lustosa study found that patients with reactions, increased disability grades and a perception of stigma had a statistically significant lower score in all scales of SF-36.

The Amharic SF-36 scores in our sample of 100 Ethiopians with leprosy were much lower compared to the Ethiopian normative data (Kebede *et al.*, 2004). The difference was more marked in the scales regarding bodily pain and social functioning. This may be because 81% of patients interviewed were on treatment for reaction, 31% were acutely unwell on the day of the interview and 46% had severe symptoms. The significant relationship between poorer quality of life and physical pain has been previously described in other studies (Costa *et al.*, 2012). The lower social scores in the social functioning of our leprosy patients may be a reflection of the stigma that exists in leprosy. The scores in both emotional and physical role scales were lower in leprosy patients indicating difficulties with work or other activities as a result of physical health and emotional problems.

The SF-36 scores in our patients with leprosy were analysed by patient categories. Generally women, younger people, single people, those living with family members, those achieving higher education levels, those on no medication (either MDT or steroids) and those who have had leprosy for longer scored better, but the difference in scores were not statistically significant. The latter finding may reflect an

acceptance of patients towards their disease as time progresses as well as the clinical explanation that patients tend to have more medical issues nearer the time of diagnosis with higher occurrence of reactions and side effects of medication. It is interesting that the only significant difference between patients on MDT and those not on it was a lower score in the social functioning scale. Could the recent diagnosis of leprosy or the monthly trips to a health facility to receive MDT be affecting their social functioning?

Differences that were statistically significant were seen in patients who were literate scoring higher in PF, RE, MH, PCS and MCS compared to those who were unable to read and write, as well in patients from urban areas scoring higher in the BP, GH, SF, MH, PCS and MCS than those from rural areas. Both literacy and residence may be markers for socio-economic status as well as access to information, health care facilities and other services. Strong correlations were found between higher grades of disability and lower SF-36 scores, in particular in PF, BP, SF, RE, MH, PCS, and MCS. The correlation between higher level of severity of symptoms and lower quality of life scores was statistically significant in all the scales of SF-36. This was also mostly true for the number of symptoms experienced and for patients who were unwell on the day of the interview.

The differences in scores in the Amharic SF-36 between patient categories described above indicate that the questionnaire has good construct validity.

We feel confident that our Amharic SF-36 is a valid and reliable instrument to measure HRQOL in clinical trials involving leprosy patients.

CHAPTER 5 SETTING UP THE CLINICAL TRIALS

Clinical trial design and methods

- **Overview**
- **Trials description**
- **Case definitions**
- **Sample size calculations**
- **Subjects and study location**
- **Consent**
- **Eligibility**
- **Exclusion criteria**
- **Randomisation**
- **Treatment regime**
- **Baseline assessment**
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- **Safety monitoring**
- **Statistical analysis**

Ethical approvals and Good Clinical Practice

Study medication

- **Study drug regimens**
- **Placebo controlled double blind study**
- **Study drug manufacturing**

Staff training

5.1 CLINICAL TRIAL DESIGN AND METHODS

5.1.1 Overview

Our hypothesis was that in the management of patients with leprosy reactions, ciclosporin is as effective as prednisolone and that it has fewer side effects than prednisolone. Four trials sharing similar methodology were designed to test this hypothesis. These are described here with the differences highlighted.

5.1.2 Trials description

Study T1RA was a randomised double blind controlled trial comparing the efficacy and safety profile of ciclosporin and prednisolone in the management of Type 1 Reactions.

Study T1RB was an open study assessing the efficacy and safety of ciclosporin as a second-line drug in patients with Type 1 Reactions who have not responded to a 12-week course of prednisolone.

Study ENLA was a pilot study conducted as a double blind controlled pilot study randomizing patients with new acute ENL to treatment either with ciclosporin or Prednisolone.

Study ENLB was a double blind controlled pilot study randomizing patients whose ENL is not controlled with standard prednisolone, and comparing a group treated with ciclosporin to a group treated with additional steroid only.

5.1.3 Case definitions

1. **Type 1 Reaction** (T1R) was diagnosed when a patient with leprosy had erythema and oedema in skin lesions and/or neuritis. A patient could have skin reaction only, a nerve reaction only or a skin and nerve reaction.
2. **Chronic Type 1 Reaction** was diagnosed when a patient was developing new erythematous skin lesions or worsening neuritis despite steroid treatment or was not managing to remain free of T1R recurrence for at least four weeks without steroid.

3. **Neuritis** was diagnosed when a leprosy patient had any of the following on history or examination:
    - Spontaneous nerve pain, paraesthesia or nerve tenderness
    - New sensory or motor impairment of recent onset
    - Mixed sensory and/or motor impairment with nerve tenderness.
4. **Nerve function impairment** (NFI) was defined as clinically detectable impairment of sensory or motor nerve function using the definitions below (van Brakel & Khawas, 1994b).
5. **New NFI** was defined as less than six months duration of reduction in sensory or motor function on history or examination.
6. **Motor loss** was defined by a decrease in voluntary muscle testing (VMT) score, by 1 point or more from the normal score of 5, using the modified MRC scale.
7. **Sensory loss** was defined by a decrease in sensation as measured by Semmes Weinstein monofilament testing. In the hands, this was defined as not being able to perceive the 0.2gm monofilament at 2 points out of 3 in each nerve of the hand. In the feet, this was defined as not being able to perceive the 2gm monofilament at 3 out of 4 sites of the foot.
8. **Erythema nodosum leprosum (ENL)** was diagnosed when a patient had crops of tender subcutaneous skin lesions. Systemic features are recorded separately and may be: fever (temperature >38°C), neuritis, joint pain, bone tenderness, orchitis, iritis, oedema, malaise, anorexia and lymphadenopathy. The timing of ENL definitions are based on previous studies (Pocaterra *et al.*, 2006).
9. **New ENL** was defined as the occurrence of ENL for the first time in a patient with lepromatous or borderline lepromatous leprosy.
10. **Recurrent ENL** was defined by the appearance of specific ENL symptoms in a patient, who has had ENL previously treated with prednisolone and has been free of ENL symptoms for four weeks off prednisolone.
11. **Chronic ENL** was defined as an ENL episode lasting more than 6 months as the patient experienced a flare-up of ENL whilst on prednisolone treatment.
12. **Silent neuropathy** (SN): A patient had silent neuropathy when he/she had sensory and/or motor impairment of recent onset (less than six months duration) in an area innervated by one or more nerve without signs of a reaction (RR or ENL) or nerve pain with or without tenderness.

13. **T1R recurrence or flare-up** was defined as an increase in skin severity score to 4 or more out of 9 AND/OR an increase in NFI defined as worsening of VMT by one point in two or more muscles, or by 2 points in one muscle and/or worsening of ST: decreased sensation in at least two out of 3 points per nerve on the hand and/or 3 or more points on the feet. NB: nerve tenderness was not part of the definition for T1R recurrence.
14. **ENL recurrence or flare-up** was defined as the appearance on new ENL nodules after initial control, either whilst on treatment or with 4 weeks of finishing treatment. NB: systemic symptoms and signs of ENL were not part of the definition of an ENL recurrence.
15. **NFI outcomes** were defined clinically as (based on (Marlowe *et al.*, 2007)):
    a. **Recovered** when the motor or sensory function returned to normal;
    b. **Improved** when the motor function improved by the VMT improving by one point in two or more muscles or by 2 points in one muscle and /or the sensory function improved by at least two out of 3 points per nerve on the hand and/or 3 or more points on the feet;
    c. **Not improved** when no changes where recorded in either VMT or ST;
    d. **Worse** when the motor function or sensory function where found to be decreased by any point on VMT and/or ST;
    e. **Remained stable after treatment** when the final assessment at week 28 or 32 showed that motor and or sensory function was similar or better compared to the end of treatment assessment at week 20;
    f. **Relapsed after treatment** when the final assessment at week 28 or 32 showed that motor and or sensory function was worse compared to the end of treatment assessment at week 20.

5.1.4 Sample size calculations

The sample sizes were calculated with Peter Nicholls, study statistician, in consultation with ALERT hospital physicians.

Type 1 reactions:

For Study 1 A (the RCT), we used the Hypothesis of Non-Inferiority. Prednisolone is known to show an improvement of about 60% in nerve function in new T1R. Given

that the true mean cure rates of the treatment agents and the active control are θ1=θ2=60%, the non-inferiority margin was selected to be δ=0.25. The sample size was calculated using a power of β=80% and significance of α=0.05, giving us a sample of n=48 in each arm respectively (Table 5.1)

α, signifance	0.05	0.05	**0.05**	0.05
β, power	80%	80%	**80%**	80%
$\theta_{1,}$ ***mean response test drug***	0.60	0.60	**0.60**	0.60
$\theta_{2,}$ ***mean response control drug***	0.60	0.60	**0.60**	0.60
δ, non-inferiority margin	0.10	0.20	**0.25**	0.30
r*, *allocation ration	1	1	**1**	1
n, ***sample size per group***	297	75	**48**	33
N, ***sample size total***	594	150	**96**	66

Table 5.1 Sample size calculation

For study 1B, the numbers recruited depended on the presentation of cases, but the aim was to recruit around 20 patients.

ENL:

We aimed to recruit at least 12 patients with new ENL to Study 2A and at least 18 patients with recurrent or chronic ENL to Study 2B. As these were pilot studies, we aimed to provide information on efficacy and safety.

5.1.5 Subjects and study location

Subjects were leprosy patients with reactions attending the Leprosy Clinic (Red Medical Clinic) based at ALERT Hospital, Addis Ababa, Ethiopia.

5.1.6 Consent

Informed consent was obtained by a native Amharic speaker after he had fully explained the trial and answered any questions. The trial consent forms and information leaflets were available in Amharic and in English. The consent forms were signed by all participants (if they were unable to sign, a mark or thumb print was used instead and witnessed by the person obtaining the consent) (Appendix 11).

5.1.7 Eligibility

The study participant had to be a confirmed leprosy case: could be newly diagnosed, currently or previously on multi-drug therapy, aged between 18 and 65 years, weigh more than 30kg and be able to give informed consent. Study specific entry criteria are described below:

- Study T1RA: Patients with newly diagnosed T1R or neuritis
- Study T1RB: Patients with T1R who have not improved after 12 weeks of steroid therapy or have had a recurrence of T1R whilst on treatment
- Study ENLA: Patients with clinical evidence of new ENL
- Study ENLB: Patients clinical evidence of recurrent or chronic ENL

5.1.8 Exclusion criteria

Exclusion criteria included patients unwilling to give informed consent or return for follow-up, as well as patients with severe active infections such as HIV and tuberculosis, or patients with renal failure, abnormal renal function, and hypertension. Women of reproductive age not willing to use contraception for the duration of the study, and pregnant or breastfeeding women, were excluded.

5.1.9 Randomisation

Block randomisation in groups of four using a table of random numbers was generated under the guidance of Dr Peter Nicholls. A standard envelope system was used for allocation concealment. The envelopes were pre-packed in Addis Ababa by Dr Rea Tschopp, a local veterinary researcher who has no association with this study. The randomization process was done for the three studies T1RA, ENLA and ENLB. The allocation procedure was operated solely by the study pharmacist at ALERT Hospital who kept a separate record of the allocation. The participants were randomly allocated to the ciclosporin or the prednisolone arm and so had an equal chance of being in either arm of the study. The pharmacist's duty included confirming patient identification and the supply of on-going medication according to treatment arm during the 20 weeks of treatment. All study participants, physicians, ward staff and other assessors (physiotherapists) were blinded to the allocation. The

pharmacist revealed the allocation code to the researchers once recruitment, follow-up, data collection and laboratory analyses had been completed (July 2013).
Each participant was assigned a unique trial number and a record of patients excluded from the studies was kept.

5.1.10 Treatment regimen

In studies T1RA, ENLA and ENLB patients were randomly allocated to receive either ciclosporin and prednisolone or prednisolone alone. The prednisolone arm followed the standard ALERT regimen starting at 40 mg and gradually decreasing, whereas the ciclosporin arm received ciclosporin 7.5mg/kg/day and 40mg oral prednisolone for the first two weeks, then two weeks of ciclosporin 7.5mg with tapering down prednisolone, followed by ciclosporin only for a total of 20 weeks (T1R) or 16 weeks (ENL), gradually tapering the dose down. The exact rationale behind the dosage of the medication and the length of treatment is described in detail in Section 5.3.1.

5.1.11 Baseline assessment

Baseline data were collected on all patients for age, sex, time since leprosy symptoms first developed, the clinical Ridley-Jopling classification of their disease, treatment with MDT and previous reactions. A detailed history of their skin and nerve symptoms was taken. The number and morphology of skin lesions, the presence of peripheral oedema, nerve tenderness, and paraesthesia or nerve pain were recorded. Nerve function impairment present for more than six months was recorded. The nerve involved and the functional modality affected (sensory or motor) was also documented.

The individual's weight, height, temperature and blood pressure were recorded. The skin was examined and the features of the skin signs including number and morphology of lesions and the presence of erythema or ulceration were recorded. The physiotherapist performed Sensory Testing (ST) using five SWMs at designated test sites on the hands and feet and Voluntary Muscle Testing (VMT) using the modified Medical Research Council grading of power. The results of the examination findings were recorded and a Clinical Severity Score calculated using the severity scale.

All individuals had the following basic examinations performed: full blood count, renal function, liver function, glucose and a stool specimen was examined for ova, cysts and parasites. Patients were given a three day course of albendazole to cover for strongyloides. Symptomatic screening for TB (cough longer than 3 weeks, other respiratory symptoms, night sweats or weight loss) was carried out as well as an HIV test following pre-test counselling. All women of reproductive age had a urine test to rule out pregnancy.

Slit skin smears to calculate the BI was taken from four sites if the participant had not had one done in the three months prior to enrolment. A skin biopsy was performed for histo-pathological confirmation of the Ridley-Jopling classification.

5.1.12 Clinical and laboratory assessments

Follow-up assessments were carried out at weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, and 32 from baseline (Table 5.2).

	Base-line	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Tot
Clinical assessment	X	X	X	X	X	X	X	X	X	X	X	**12**
Renal function	X	X	X	X	X	X			X			**7**
FBC, LFT	X			X		X			X			**3**
Glucose (glucometer)	X	X	X	X	X	X	X	X	X	X		**10**
Stool + PRN	X					X			X			**1**
Urinalysis - PRN	X		X		X	X	X		X			
HIV	X					X			X			**3**
Pregnancy test	X		X		X	X	X	X	X			**7**
TB screen	X											
Skin Biopsy	X						X					**2**

Table 5.2 Summary of investigations done on study patients

Clinical assessment consisted of focussed questions about skin, nerve function and possible drug adverse effects; a general physical examination and a record of specific T1R and ENL signs. Patients were also examined for new skin lesions, evidence of new nerve function impairment (NFI) using monofilaments for sensory testing and MRC scale for voluntary muscle testing (VMT). Weight was measured at each review and the dose of Ciclosporin adjusted accordingly. Blood pressure was measured at each visit. Blood glucose and dipstick urinalysis for glucose and protein were done at each review. Blood tests (full blood count, renal function, liver function and HIV test) were carried out at specified times. The full Standard Operating Guidelines (SOP) are in Appendix 12.

5.1.13 Data recording and management

All data were recorded at each assessment on standardised patient record forms (PRF) - Appendix 13. The study forms were kept in a separate set of case notes from the ordinary hospital record. All study records were kept in a locked area accessed only by two nominated study staff. The data were then verified and entered into case record forms (CRF) by the study physicians. First data entry into the secure anonymised Microsoft Office Access 2007 database was done by me and the second entry by one of the data managers at ALERT/AHRI. The double entry was then verified using Epi-Info 3.5.4. The initial rate of errors detected by double entry was just under 10%. Errors in the data were verified and corrected in Ethiopia.

5.1.14 Outcome measures

The outcome measures being compared between the patients recruited to the two different treatment arms vary slightly for the T1R and ENL studies.

1. **Study T1RA**

   Primary outcome: Change in clinical nerve function impairment and Clinical Severity Score at week 4, 20, and 28.

   Secondary outcomes:

1. Mean time to recurrence of T1R for patients in each treatment arm
2. Number of T1R recurrence episodes per patient in each treatment arm:
    a. Whilst on treatment (week 1-20)
    b. During follow-up (week 21- 32)
3. Severity of T1R recurrence for patients in each treatment arm:
    a. Whilst on treatment (week 1-20)
    b. During follow-up (week 21- 32)
4. Amount of extra prednisolone for patients in each treatment arm:
    a. Whilst on treatment (week 1-20)
    b. During follow-up (week 21- 32)
    c. Total
5. Frequency of adverse events in patients in each treatment arm
6. Difference in score in Quality of Life assessment between start and end of treatment for patients in each treatment arm

2. Study T1RB

The outcomes and analysis was the same as for study T1RA, without the comparison group. This group added additional information on adverse effects of ciclosporin, as well as information on efficacy of ciclosporin as a second line treatment.

3. Studies ENLA and ENLB

Primary outcome: Number of ENL recurrence episodes per patient for each treatment arm:

a. Whilst on treatment (week 1-16)
b. During follow-up (week 17- 32)

Secondary outcomes:

1. Mean time to ENL recurrence after initial control for patients in each treatment arm
2. Severity of ENL at recruitment and at recurrence for patients in each treatment arm:

a. Whilst on treatment (week 1-16)
b. During follow-up (week 17- 32)

3. Amount of extra prednisolone for patients in each treatment arm:
    a. Whilst on treatment (week 1-16)
    b. During follow-up (week 17- 32)
    c. Total
4. Frequency of adverse events for patients in each treatment arm
5. Difference in score in Quality of Life assessment between start and end for patients in each treatment arm

5.1.15 Safety monitoring

It is essential that all adverse events which occur during the course of study in a research project are appropriately recorded and reported in order to ensure the continuing safety of the participants.

There are internationally agreed guidelines on adverse event reporting in clinical trials. A reporting system was put in place with adverse events reported in a timely manner to the DSMB and the sponsor of the trial. In a double blinded trials this becomes even more important, as it is difficult to assess causality. Each adverse event was evaluated for seriousness, causality, expectedness and severity. We used the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE, 2008) in this study as a system to grade each adverse event.

An adverse event was defined as serious if it:

- resulted in death
- was life-threatening
- required hospitalisation, or prolongation of existing in-patients' hospitalisation.
- resulted in persistent or significant disability or incapacity
- was a congenital anomaly or birth defect

Causality could vary from unrelated to definitely related and the various degrees of causality are described in Table 5.3. Expectedness or unexpectedness related to whether the adverse event or reaction had been previously reported as being related to that study drug or had been recorded in the Summary of Product Characteristics. Severity was categorised either as mild/moderate/severe or with a numerical grading for severity with correlating descriptive or numerical values.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing fact.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Table 5.3 Description of causality of adverse events in drug trials

Consequently, AEs were classified into different categories (definitions are in SOP-Appendix 12):

1. Adverse Event
2. Adverse Reaction
3. Serious Adverse Event/Reaction
4. Suspected Serious Adverse Reaction
5. Suspected Unexpected Serious Adverse Reaction

Prednisolone and ciclosporin study

A set of minor and major events related to prednisolone (Richardus *et al.*, 2003b), was defined during a study on the effect of prednisolone on long-standing NFI in leprosy. These are listed below:

- Major adverse events
  i. Peptic ulcer
  ii. Diabetes mellitus
  iii. Psychosis or other mental health problems
  iv. Glaucoma
  v. Cataract
  vi. Hypertension >160/90 on two separate readings at least one week apart
  vii. Infections
  viii. Infected ulcers
  ix. Corneal ulcer
  x. Tuberculosis
- Minor adverse events
  i. Moon face
  ii. Acne
  iii. Cutaneous (including nails)fungal infections
  iv. Gastric pain requiring antacids

All other possible or expected side effects related to prednisolone are described in greater detail in Chapters 2.3.2 and 2.3.3 (6) as well as Appendix 2.

Few ciclosporin side effects were seen in the pilot study conducted by S. Marlowe (Marlowe *et al.*, 2007) on the effect of ciclosporin on T1R. The possible side effects of ciclosporin are described in detail in the drug information leaflet in Appendix 3 and in Chapter 2.3.5. Adverse events monitored for included: gum hyperplasia, convulsions, peptic ulcers, pancreatitis, fever, vomiting, diarrhoea, confusion, breathing difficulties, pruritus, high blood pressure, potassium retention and possibly hyperkalaemia, kidney and liver dysfunction (nephrotoxicity & hepatotoxicity), and an increased vulnerability to opportunistic fungal and viral infections. A specific table was developed to detect anticipated adverse effects for both ciclosporin and

prednisolone (Table 5.4). Detailed history, examination and laboratory investigations were designed to monitor any side effects.

Symptoms or signs to monitor	
Moon face	□
Acne	□
Gum hyperplasia	□
Cutaneous (including nails) fungal infections	□
Gastric pain requiring antacid	□
Gastrointestinal bleeding	□
Nocturia, polyuria, polydipsia	□
Diabetes mellitus	□
Psychosis or other mental health problems	□
Weight loss >5kg	□
Weight gain	□
Glaucoma	□
Cataract	□
Hypertension BP > 160/90 on 2 separate readings at least 1/52 apart	□
Infections	□
Infected ulcers	□
Corneal ulcer	□
Tuberculosis	□
Night sweats	□
Convulsions	□
Vomiting	□
Diarrhoea	□
Breathing difficulties	□
Abnormal blood results (hyperkalaemia, abnormal LFT)	□
Pruritus	□

Table 5.4 Enquiry list for minor and major side effects related to ciclosporin and prednisolone

Many of the symptoms can occur with either drug, and as the study was blinded, it was difficult to decide on causality at times. Specific steps to manage adverse events without resorting to un-blinding were designed (Table 5.5 and Table 5.6).

Rather than un-blinding as soon as abnormal laboratory or clinical parameter was suspected to be linked to ciclosporin, a message was given to the study pharmacist to adjust the dose if patient was on ciclosporin and close observation was instituted.

Adverse events were recorded on the PRF and a special form had to be completed for any SAE (Appendix 14). SAEs were reported to the DSMB either by phone or email

as soon as possible after the event. A more detailed case presentation was given during the six monthly meeting. Criteria for un-blinding were set out in the Standard Operating Procedures (SOP).

Clinical Parameter	Level	Action
Blood Pressure	If BP> 100mg diastolic after maximal antihypertensive therapy	Stop Cn
	If BP moderately elevated	Reduce ciclosporin by 25% or introduce anti-hypertensive (avoid K+ sparing agent – may cause hyperkalaemia)
Gingival overgrowth	Severe	Reduce Cn by 1mg/kg
Hypertrichosis	Noticeable but not unacceptable to patient	Reassure and continue Cn
Hypertrichosis	Unacceptable to patient	Stop Cn
Nausea and vomiting	Mild, treatable	Anti-emetics
Nausea and vomiting	Severe	IV rehydration STOP Cn
Diarrhoea	Severe (every hour and leading to dehydration)	Stop Cn and restart dose reduced by 1mg/kg after dehydration resolved
Malaise		Measure Potassium
Gastric pain		Antacids/ Ranitidine

Table 5.5 Guidance for managing clinical symptoms in ciclosporin/ prednisolone trials in leprosy reactions

Laboratory parameter	Level	Action
Serum creatinine	If level increases more than 30% above baseline, on more than 1 measurement	Reduce dose of ciclosporin by 1mg/kg
	If level increases more than 50% above baseline	Reduce dose of ciclosporin by 50%
	If still >50% above baseline after 1 month of halved dose	STOP ciclosporin. May need un-blinding.
Serum potassium	5.0 – 6.4mmol/l	Reduce ciclosporin dose by 1mg/kg. Repeat Potassium after 2 days. If still in this range then reduce dose by 1mg/kg and repeat blood test every 2 days until within normal level
	>6.4mmol/l	STOP ciclosporin. Five 50ml of 50% IV dextrose plus 5 units of Actrapid over 20 minutes followed by 1 litre 10% dextrose IV given over 12 hours. Repeat serum Potassium the following day and every 2 days after until within the normal range. Un-blind.

Table 5.6 Guidance for managing abnormal laboratory parameters

5.1.16 Statistical analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS version 20. SPSS Inc., Chicago, Illinois). An intention to treat analysis was used for calculating the effects of treatment on individuals in each group. As the data in the small studies ENL are not normally distributed, non-parametric tests were used to assess statistical significance. In the T1Rstudies, t tests and ANOVA (analysis of variance) were used as appropriate. The Mann-Whitney U test was used for all statistical tests of continuous variables and Fisher's exact test was used to compare dichotomous variables.

5.2 ETHICAL APPROVALS AND GOOD CLINICAL PRACTICE

With the changes in the system at ALERT and the general health system in Ethiopia, obtaining ethical approval for this clinical trial became challenging. New regulations were being put into place and rapid staff change-over in Ethiopia slowed down any decision making. It took just over a year to obtain all the Ethical approvals listed below (Appendix 15):

1. London School of Hygiene and Tropical Medicine Ethics Committee, approval numbers: 5376, 5377 and 5378
2. AHRI/ALERT Ethical Review Committee, project number: P005/08
3. National Science and Technology Ethics Review Committee of Ethiopia approval number: RDHE/34-90/2009
4. Drug Administration and Control Authority of Ethiopia, clinical trial authorization reference number: 02/12/79/926.

The trials were registered at ClinicalTrials.gov: NCT00919815, NCT00919451, NCT00919542 and NCT00919776. Insurance was also obtained.

Good Clinical Practice (GCP) is an international quality standard that is provided by the International Conference on Harmonisation (ICH), an international body that defines standards which governments can transpose into regulations for clinical trials

involving humans. GCP enforces tighter guidelines on ethical aspects of a clinical study, comprehensive documentation for the clinical protocol, record keeping, training and safe record storage. The main aim of GCP is to provide investigators and their study team with the tools to protect human subjects and collect good quality data.

I undertook two courses in GCP in London and in Ethiopia. Prior to starting the ciclosporin clinical trial, I organized a GCP course for all the staff at ALERT involved in the trial. Qualified GCP trainers were supplied by AHRI and the training timetable is attached (Appendix 16). An independent data and safety monitoring board (DSMB) was appointed to monitor patient safety and treatment efficacy data whilst the trial was going on, and met every six months. Terms of reference were drawn up according to the WHO Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards for Research and Training in Tropical Diseases (WHO-TDR 2005). Serious adverse events were reported to DSMB as soon as possible after their occurrence.

The three members of the DSMB were:

1. Dr Fuad Temam – Consultant Dermato-pathologist, Kadisco Hospital
2. Dr Girmay Medhin – Physician with clinical trial experience, Aklilu Lemma Institute of Pathobiology, Addis Ababa University
3. Dr Getnet Yimer – Bio-Statistician, Department of Pharmacology, Addis Ababa University

A qualified WHO clinical trial monitor, Dr Martha Tibebu, was also appointed.

5.3 STUDY MEDICATIONS

Prednisolone and ciclosporin were the two study drugs in our clinical trials.

5.3.1 Study drug regimens

In the two Marlowe pilot studies, the dose of ciclosporin used was 5mg/kg/day. Trough level of ciclosporin was measured in 42 patients with T1R. The overall mean

trough level was 361 ng/ml (range 86—764 ng/ml) for the nine Nepalis and 352 ng/ml (range 70—1004 ng/ml) for the 33 Ethiopians. Fifteen Ethiopians required an increased ciclosporin dose due to undetectable clinical improvement, and five (33%) of these patients had a mean ciclosporin level of 60 ng/ml (range 32-77ng/ml) prior to dose increase. However, the other ten (67%) patients meeting clinical criteria for increased ciclosporin dose had a mean ciclosporin level of 307ng/ml (range 108-799 ng/ml) at the time of showing no clinical improvement. The mean ciclosporin level for Ethiopian patients on the increased dose of 7.5mg/kg/day was 751 ng/ml (range 130-1787ng/ml). In addition, the time that a reduction in trough level was found corresponded with a worsening in nerve function impairment for these patients. The study concluded that ciclosporin trough measurements are not needed in resource-poor settings as these only indicated patient treatment compliance and had no correlation with clinical outcome.

The study recommended using higher doses of ciclosporin (7.5mg/kg/day) in future studies, longer periods of treatment, as well as tapering the drug slowly or adding low dose prednisolone to prevent relapse.

The onset of action of ciclosporin is between four to eight weeks after initiation of therapy (Nast *et al.,* 2013) and it is usually prescribed in combination with prednisolone to cover the slow onset of action especially in organ transplantation (Lindholm *et al.,* 1993). As the disposition of ciclosporin from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5 to 18 hours), it is given twice a day. In comparison, prednisolone shows peak effects 1-2 hours after ingestion and has a half- life of 18-36 hours. In Marlowe's study, patients were started on ciclosporin 5mg/kg/day and 40mg of prednisolone for the first five days only. Patients were continued on ciclosporin only for a total 12 weeks and, in the Ethiopian cohort, 33% of patients required the increased dose of 7.5mg/kg/day, because of clinical deterioration.

We theorized that given the slow onset of action of ciclosporin compared to prednisolone and high relapse rate of T1R, the most effective regimen in leprosy reaction would be an initial ciclosporin dose of 7.5mg/kg/day, divided in two doses, gradually tapered down over a total period of 20 weeks and adding prednisolone cover for the first four weeks of treatment.

The TIR patients on the prednisolone arm would get 20 weeks of a gradually reducing course of prednisolone only. This is the prednisolone regimen recommended by the Rao trials (Rao *et al.*, 2006). The final regimen agreed upon is shown in Table 5.7.

	Prednisolone alone arm	**Ciclosporin and Prednisolone arm**
Week 1	Prednisolone 40mg+ PC*	Ciclosporin 7.5mg/kg + Prednisolone 40mg
Week 2	Prednisolone 40mg + PC	Ciclosporin 7.5mg/kg + Prednisolone 40mg
Week 3	Prednisolone 35mg + PC	Ciclosporin 7.5mg/kg + Prednisolone 20mg
Week 4	Prednisolone 35mg + PC	Ciclosporin 7.5mg/kg + Prednisolone 10mg
Wk 5 & 6	Prednisolone 30mg + PC	Ciclosporin 7.5mg/kg + PP**
Wk 7 & 8	Prednisolone 25mg + PC	Ciclosporin 7.5mg/kg + PP
Wk 9-12	Prednisolone 20mg + PC	Ciclosporin 7.5mg/kg + PP
Wk13-16	Prednisolone 15mg + PC	Ciclosporin 6mg/kg + PP
Wk17-18	Prednisolone 10mg + PC	Ciclosporin 4mg/kg + PP
Wk19-20	Prednisolone 5mg + PC	Ciclosporin 2mg/kg + PP

*PC=placebo ciclosporin; **PP= placebo prednisolone

Table 5.7 Treatment protocol for T1R studies

For the ENL pilot studies the same principles as above were used, adjusting the length of treatment of ENL to the 16 weeks period in the local ALERT guidelines. The regimen is shown in Table 5.8.

	Prednisolone alone arm	**Ciclosporin and Prednisolone arm**
Week 1	Prednisolone 60mg +	Ciclosporin 7.5mg/kg + Prednisolone 40mg
Week 2	Prednisolone 55mg + PC	Ciclosporin 7.5mg/kg + Prednisolone 40mg
Week 3	Prednisolone 50mg + PC	Ciclosporin 7.5mg/kg + Prednisolone 20mg
Week 4	Prednisolone 45mg + PC	Ciclosporin 7.5mg/kg + Prednisolone 10mg
Week 5	Prednisolone 40mg + PC	Ciclosporin 7.5mg/kg + PP**
Week 6	Prednisolone 35mg + PC	Ciclosporin 7.5mg/kg + PP
Week 7	Prednisolone 30mg + PC	Ciclosporin 7.5mg/kg + PP
Week 8	Prednisolone 25mg + PC	Ciclosporin 6mg/kg + PP
Week 9	Prednisolone 20mg + PC	Ciclosporin 6mg/kg + PP
Week 10	Prednisolone 20mg + PC	Ciclosporin 6mg/kg + PP
Week 11	Prednisolone 15mg + PC	Ciclosporin 4mg/kg + PP
Week 12	Prednisolone 15mg + PC	Ciclosporin 4mg/kg + PP
Week 13	Prednisolone 10mg + PC	Ciclosporin 3mg/kg + PP
Week 14	Prednisolone 10mg + PC	Ciclosporin 3mg/kg + PP
Week 15	Prednisolone 5mg + PC	Ciclosporin 2mg/kg + PP
Week 16	Prednisolone 5mg + PC	Ciclosporin 1mg/kg + PP

*PC=placebo ciclosporin; **PP= placebo prednisolone

Table 5.8 Treatment protocol for ENL studies

Weight adjusted medication cards for each treatment arm were designed for the pharmacist, using a 10 kilogram range in patient weight. Examples of these are shown in Appendix 17.

5.3.2 Placebo controlled double blind study

It was difficult to get similar looking prednisolone and ciclosporin capsules or tablets, so that two different placebo were required to blind the study. The prednisolone only regimen contained ciclosporin placebo capsules ("PC"), to equalize tablet numbers and twice daily regimes. The ciclosporin placebo looked exactly like the active ciclosporin brown capsule but had no active ingredients. The ciclosporin arm regimen contained prednisolone placebo tablets ("PP"). The prednisolone placebo looked exactly like the active prednisolone pink tablet but had no active ingredients. This was essential for blinding patients and doctors. Every patient ended up taking a varying combination of brown capsules twice a day and a number of pink tablets every morning.

5.3.3 Prescribing additional prednisolone

Criteria for using additional prednisolone were defined as:

- Sustained deterioration for a period of at least two weeks of:
- Deterioration in nerve function
- Nerve pain unresponsive to analgesics
- Palpable swelling of skin patches
- New erythematous and raised skin patches
- Deterioration in nerve function which the study doctors believe requires immediate additional prednisolone
- ENL flare-up with the appearance of new subcutaneous nodules

Regimen for additional prednisolone depended on the study into which the patient had been recruited and the time at which the reaction flare-up occurred. If there was a recurrence of severe T1R with or without NFI during treatment period in the open

study, then adding extra prednisolone to make up a total of 40mg, then tapering according to the original regimen was done.

For patients recruited into the double-blinded studies T1RA, ENLA or ENLB, the clinician would be unable to know whether the patient was on the prednisolone or ciclosporin arm, additional rules were agreed upon. If the reaction recurrence was within the first ten weeks of treatment or there was facial involvement, extra prednisolone was added to make up a total of 40mg (with the pharmacist deciding on the exact additional dose of prednisolone required) and then tapered according to the original regimen. If T1R recurrence was after the first ten weeks of treatment, then prednisolone 20mg was added and tapered down according to the original regimen. The physician could prescribe more additional prednisolone if the reaction was severe.

5.3.4 Study drug manufacturing

After an internet search for ciclosporin manufacturers throughout the world we settled on using the same supplier as the Marlowe study, because of previous experience and reasonable cost. Ciclosporin manufactured by Panacea-Biotec, a large Indian drug manufacturer with recognized good manufacturing practice (GMP) certificates, was imported. Import permit for both the ciclosporin and the placebo capsules had to be obtained from the Ethiopian Drugs Administration and Control Authority (Appendix 18).

Prednisolone is made in Addis Ababa by E-PHARM, a drug manufacturing company belonging to the Ethiopian government. Pink tablets of 5mg prednisolone have been used in Ethiopia for a long time for leprosy reactions. The prednisolone tablets and the prednisolone placebo for this study were both produced by E-PHARM and were tested at the LSHTM drug testing unit for active ingredient content and purity (Appendix 19).

To minimize errors a full pharmacy SOP was designed covering the following topics:

- Inventory Control/Management
- Storage and Handling of Study Product
- Study Product Dispensing

- Record Keeping Responsibilities
- Monitoring and Quality Assurance
- Study Blinding and Randomization
- Protocol Deviations

5.4 STAFF TRAINING

Study staff from the ALERT leprosy clinic, laboratory, pharmacy and physiotherapy received regular training and updates throughout the study. Any errors were discussed as a team in order to minimize recurrence. Inter-tester validity in trial settings is important (Roberts *et al.*, 2007). The three study physiotherapists had to undergo inter-tester reliability exercises in order to validate their VMT/ST assessments. This was done at the beginning of the study and every six months to maintain standards. Five patients were randomly selected and underwent VMT/ST assessments by two different physiotherapists independently, within an hour of each other. The results were then compared and discussed, and the exercise repeated with a different set of patients until nearly 90% concordance was achieved.

CHAPTER 6 RESULTS OF T1R STUDIES

Results for double-blind RCT in patients with newly diagnosed T1R (T1RA)

1. **Participants**

   General characteristics
   Reaction type
   Duration and severity of T1R
   Incomplete follow-up up
   Nerve involvement

2. **Primary Outcome**: Change in Clinical Severity Score and nerve function impairment

3. **Secondary outcomes**:

   Mean time to recurrence of T1R
   Number of T1R recurrence episodes
   Severity of T1R
   Amount of extra prednisolone
   Adverse Events
   Quality of Life

4. **Summary of findings for T1RA**

Results for open study trialling ciclosporin in patients with chronic T1R (T1RB)

1. Participants
2. Primary Outcome
3. Secondary outcomes
4. Summary of findings for T1RB

Discussion of ciclosporin in T1R studies

Results of the two studies involving patients with Type 1 Reaction (T1R) are presented here. Patients with newly diagnosed T1R were randomized to 20 weeks of treatment with either ciclosporin or prednisolone in a double blind controlled trial (T1RA). Patients who had had recurrent or chronic T1R and received prednisolone for longer than 6 months, were given ciclosporin in an open study (T1RB). Patients who received ciclosporin were also given prednisolone for the first four weeks of their treatment to cover for the slow onset of action of ciclosporin. Following the 20 weeks of treatment (intervention period), patients were monitored for three months (follow-up period). Both the efficacy and safety of ciclosporin in comparison to prednisolone were analysed.

A Type 1 Reaction (T1R) was diagnosed when a patient with leprosy had erythema and oedema in skin lesions. This may have been accompanied by neuritis and oedema of the hands, feet and face. A patient could have skin reaction only, a nerve reaction only or a skin and nerve reaction. Reaction in the nerve was characterised by spontaneous nerve pain, paraesthesia or tenderness with or without nerve function impairment.

Nerve function impairment (NFI) is defined as clinically detectable impairment of motor, sensory or autonomic nerve function (van Brakel & Khawas, 1994b). New NFI is defined as less than 6 months duration.

In this study motor loss was defined by a decrease in voluntary muscle testing (VMT) score, by 1 point or more from the normal score of 5, using the modified MRC scale. Sensory loss was defined by a decrease in sensation as measured by Semmes Weinstein monofilament testing. In the hands, this was defined as not being able to perceive the 0.2gm or heavier monofilament at 2 points out of 3 in each nerve of the hand. In the feet, this was defined as not being able to perceive the 2gm monofilament at 3 out of 4 sites of the foot.

6.1 RESULTS OF DOUBLE-BLIND RCT IN PATIENTS WITH NEWLY DIAGNOSED T1R (STUDY T1RA)

6.1.1 Participants

Seventy three patients with new T1R were enrolled into trial T1RA between 12th August 2011 and 25th December 2012. The final assessment was completed on 24th July 2013. Thirty five individuals were randomized to the ciclosporin arm, and 38 to the prednisolone arm (

Figure **6.1**). Intention to treat analysis was used.

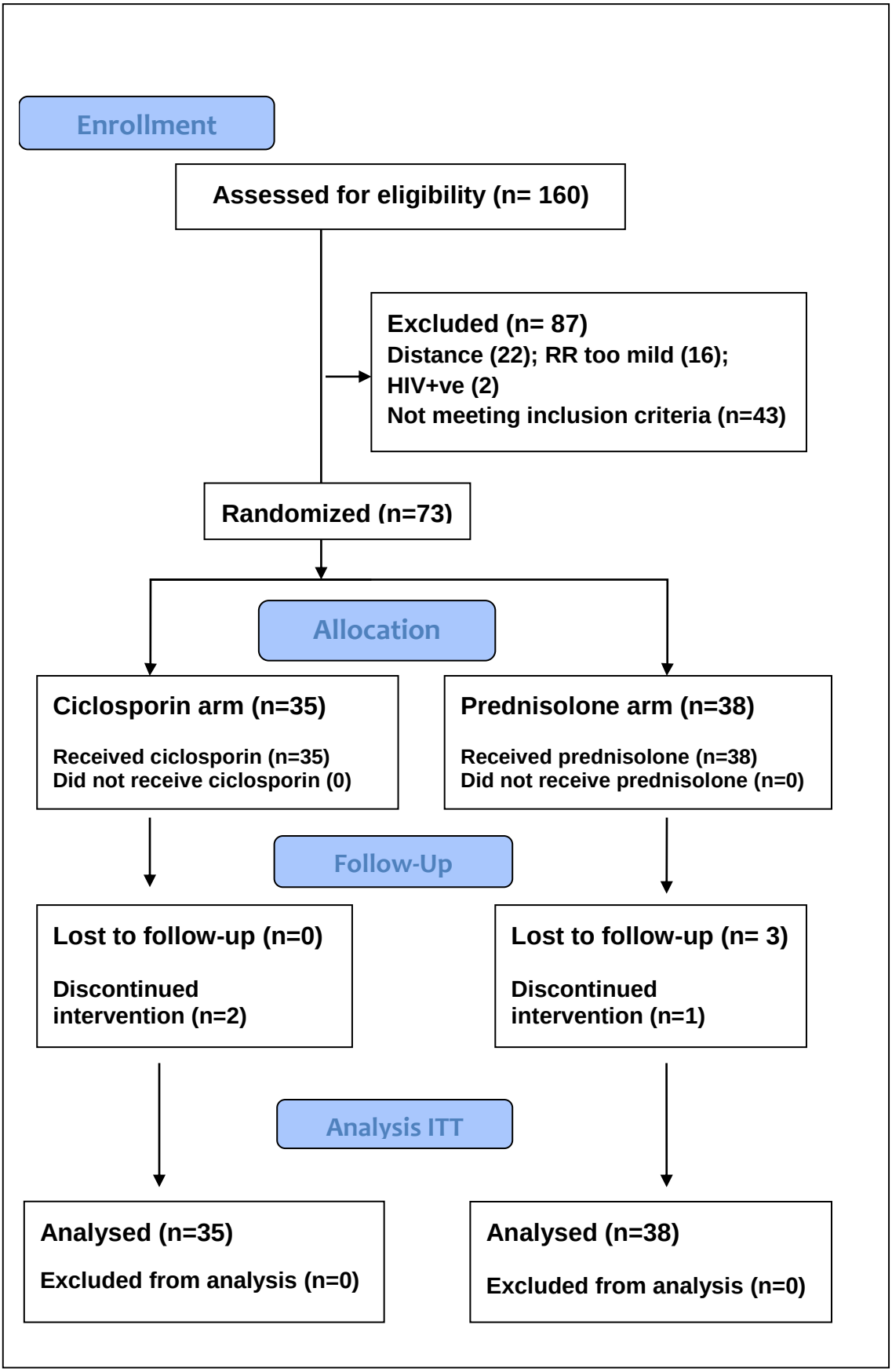


Figure 6.1 CONSORT diagram for T1RA study

General characteristics

The two groups of patients with new T1R were not significantly different with respect to sex, age, Ridley-Jopling classification, or treatment with MDT (Table 6.1).

Participants with new T1R		Ciclosporin (n=35)	Prednisolone (n=38)
Sex	Women: men	7:28	8:30
Median age (years)		27	34
Median weight (kg)		52	54
Clinical Ridley- Jopling classification	TT	0	1
	BT	27	23
	BB	2	6
	BL	5	7
	LL	0	1
	PNL	1	0
Mean BI*	at diagnosis	0.7	0.9
	at recruitment	0.2	0.1
MDT status	Started at enrolment	25	22
	Current	4	7
	Completed	6	9
Co-morbidities		2 foot ulcer 2 skin ulcers 2 fungal infections 2 conjunctivitis 1 intrahepatic cholecystiasis	1 Foot ulcer 3 skin ulcer
EHF score (mean)		3.94	3.84

**Mean BI= group mean of each patient's mean BI; PNL= pure neural leprosy*

Table 6.1 Description of study participants in each arm of T1RA study

Of the 73 participants, 50 had BT leprosy (70% had a negative BI) and 12 patients had BL leprosy. Of all participants presenting with T1R, 64% were newly diagnosed with leprosy. In these patients the signs and symptoms of the reaction were the reason for seeking medical assistance.

Reaction type

The two groups did not differ significantly in respect of reaction type, or mean number of enlarged and tender nerves per patient (Table 6.2). There was a significant difference in the duration of NFI between patients recruited to the two groups (Chi Square, p=0.039). Twice as many patients in the ciclosporin arm reported isolated

new NFI but in the prednisolone arm, there were more patients reporting combination of old and new NFI

Participants with new T1R		Ciclosporin (n=35)	Prednisolone (n=38)	P value
Reaction type	Skin only	4	8	0.541
	Skin and nerves	28	27	
	Nerve only	3	3	
Facial patches		29	25	0.164
Peripheral Oedema		30	28	0.414
Reported NFI at baseline	None	3	9	0.039
	New	20	10	
	Old	4	4	
	Mixed old and new	8	15	
Mean number of enlarged nerves per patient		9	8.5	0.306
Mean number of tender nerves per patient		4.7	3.6	0.168

Table 6.2 Reaction type and nerve involvement in study participants

Type 1 reaction occurring in both skin and nerves was present in 75% of participants, whilst 16% had reaction affecting skin only and 8% nerves only. 74% of patients had inflamed facial patches and 80% had peripheral oedema on examination.

Duration and severity of T1R

Patients in the two treatment arms had similar duration of reported T1R symptoms prior to presenting at the clinic (p=0.2). Severity of T1R, assessed both by specialist opinion and by the Clinical Severity Score, was not significantly different between the two groups (Table 6.3)

Participants with new T1R		Ciclosporin (n=35)	Prednisolone (n=38)	P value
Reported mean duration of T1R symptoms (days)		61.5 (6-180: median 58)	49.6 (5-150: median 44)	0.2
Severity by specialist opinion	Moderate	1	3	0.667
	Severe	34	35	
Severity by Clinical Severity Score (mean)	Score A (skin)	5.74	5.11	0.19
	Score B (sensation)	8.53	7.77	0.53
	Score C (motor)	9.37	6.92	0.58
	Total CSS score	22.96	19.79	0.36

Table 6.3 Duration and severity of T1R in study participants

Nerve involvement

The 73 patients recruited had a total of 876 peripheral nerves examined. Nerve function impairment of less than 6 months duration (new NFI) was reported for 308 nerves (35%). A further 24% of nerves were reported to have been impaired for longer than 6 months (old NFI). In both old and new NFI, sensory loss was more frequent than motor loss or mixed loss. 72% of nerves were enlarged, and nerve tenderness was present in 34% of nerves. Table 6.4 shows that a larger proportion of nerves were impaired in the ciclosporin group patients (68% vs. 52%) and this group had significantly higher proportion of purely sensory and mixed sensory/motor types of new NFI (p=0.0387).

Participants with new T1R		Ciclosporin (n=35)	Prednisolone (n=38)	P value
Number of nerves (n=876)		420 nerves	456 nerves	
Nerve enlargement		319 (76%)	314 (69%)	0.168
Nerve tenderness		167 (40%)	133 (29%)	0.306
Normal nerves (no sensory or motor loss)		136 (32%)	218 (48%)	
Impaired nerves		284 (68%)	238 (52%)	
Reported new NFI pattern in impaired nerves	Sensory	89 (31%)	40 (17%)	
	Motor	41 (14%)	45 (19%)	0.0387
	Mixed	59 (21%)	34 (14%)	
Reported old NFI pattern in impaired nerves	Sensory	63 (22%)	90 (39%)	
	Motor	7 (3%)	8 (3%)	0.3503
	Mixed	25 (9%)	21 (8%)	

Table 6.4 Nerve involvement in study participants with new T1R

The ulnar nerves were found to be both the most frequently enlarged and tender nerves, followed by the lateral popliteal, radial cutaneous and posterior tibial nerves. Nerve tenderness was present in 300 nerves and was more common in the ciclosporin group (40% vs. 29%) (Figure 6.2).

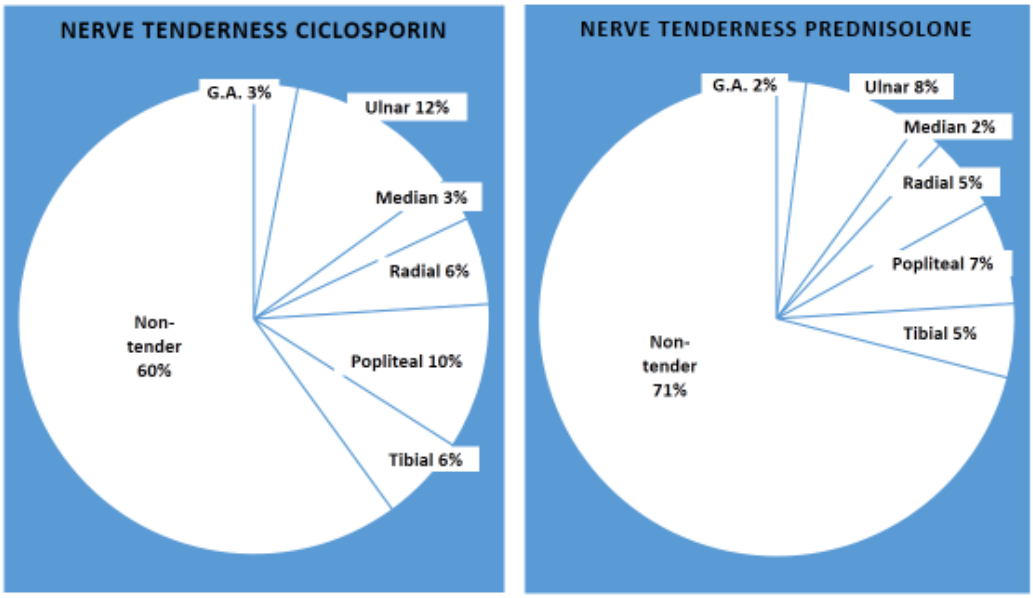


Figure 6.2 Proportion of nerves with or without nerve tenderness

Apart from a higher number of affected sensory nerves in the ciclosporin group, there was no major significant difference between the two groups of patients with newly diagnosed T1R, recruited to the study.

Incomplete follow-up

Six patients did not complete the intervention medication. Three patients in the prednisolone arm did not attend for review at week 2 or 4. One other patient in the prednisolone arm had a serious adverse event which led to un-blinding at week 6. He was removed from the study on his request and continued to take prednisolone at a different facility. Two patients in the ciclosporin arm were discontinued from the study, one for non- adherence at week 12, and the second patient had a serious adverse event on week 6 which necessitated un-blinding and discontinuation of ciclosporin. He continued the study on prednisolone.

6.1.2 Primary outcome

Change in Clinical Severity Score and nerve function impairment

The Clinical Severity Score (21 items; range of 0-63) was used to assess reaction severity. The maximum score possible for skin (A), sensation (B) and motor function (C) are 9, 24 and 30 respectively. Mild T1R is characterised by a score of 4 or less; moderate T1R by a score between 4.5 and 8.5 and severe T1R is a score of 9 or more.

Figure 6.3 shows the changes in the group mean Clinical Severity Score over time for patients in each arm of Study T1RA. Changes in the three sub-scores are also shown. Variation in group mean T1R severity scores during the 32 weeks and between the two treatment arms, was assessed by ANOVA. Patients in both treatment arms had large and statistically significant improvement with time in all four scores ($p<0.000$). This is consistent with a good clinical response with both treatments.

There was no significant difference in all four severity scores between the two treatment arms over the 32 weeks (Score A, $p=0.241$; Score B, $p=0.664$, Score C, $p= 0.749$ and Clinical Severity Score, $p=0.531$).

In the ANOVA week by week breakdown, patients on the ciclosporin arm showed significantly higher skin score (A), at weeks 6 and 8 ($p<0.000$). This was probably due to a greater number of patients in the ciclosporin arm experiencing a flare-up in skin reaction at this time.

The difference between the two treatment groups in median improvement of Clinical Severity Scores were compared at week 0, 4, 6, 20, and 28 is shown in Figure 6.4. These time periods were deemed important, as at week 4, the prednisolone in the ciclosporin in stopped, at week 20 the intervention period ends, and week 28 represents the end of the study.

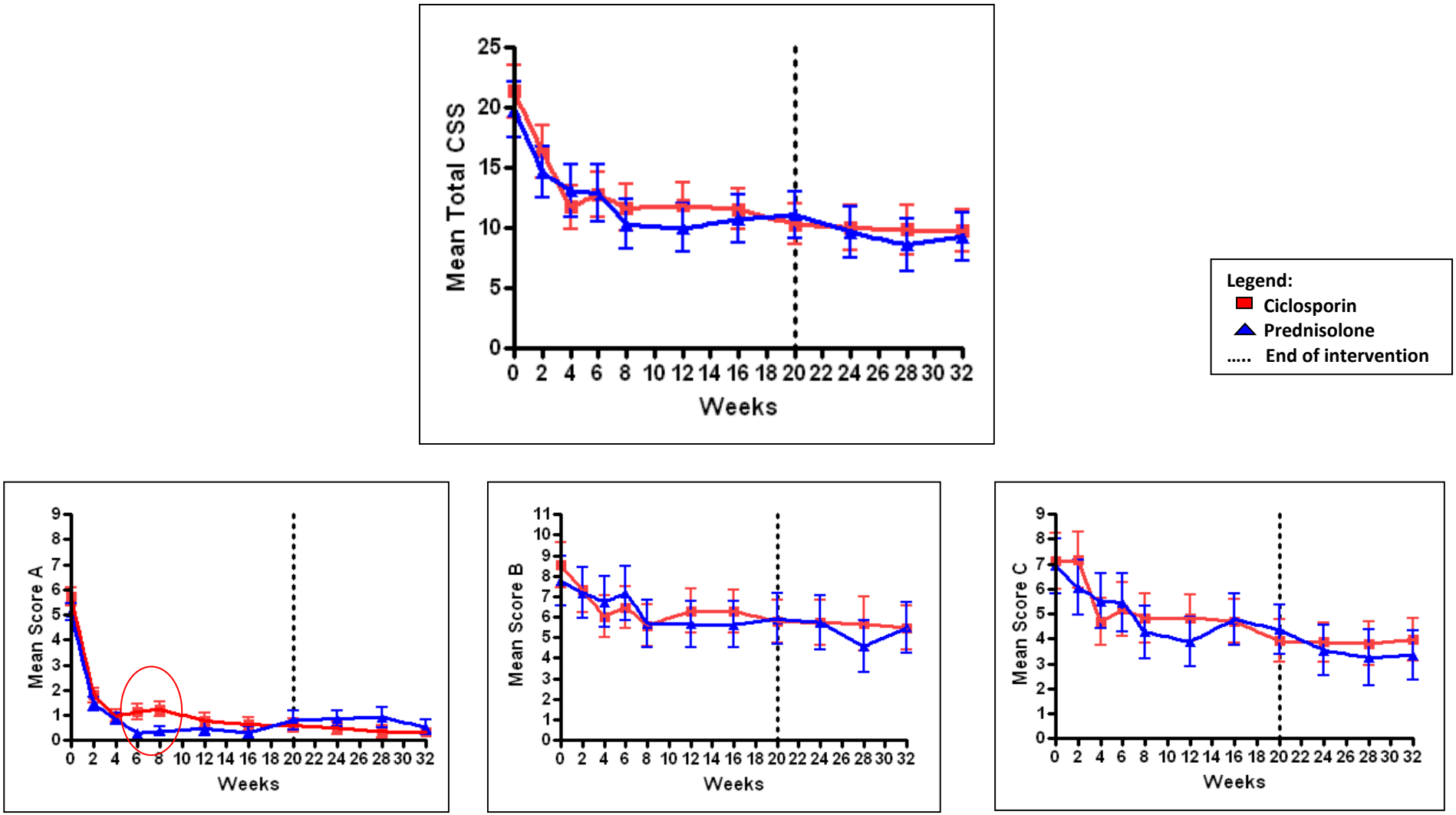


Fig 6.3 Group mean and standard error in Clinical Severity Scores for T1R patients by treatment arm; with breakdown for Score A (skin), Score B (sensation) and Score C (motor). *(0 marks the area in Score A where the difference between the treatment arms is significant)*

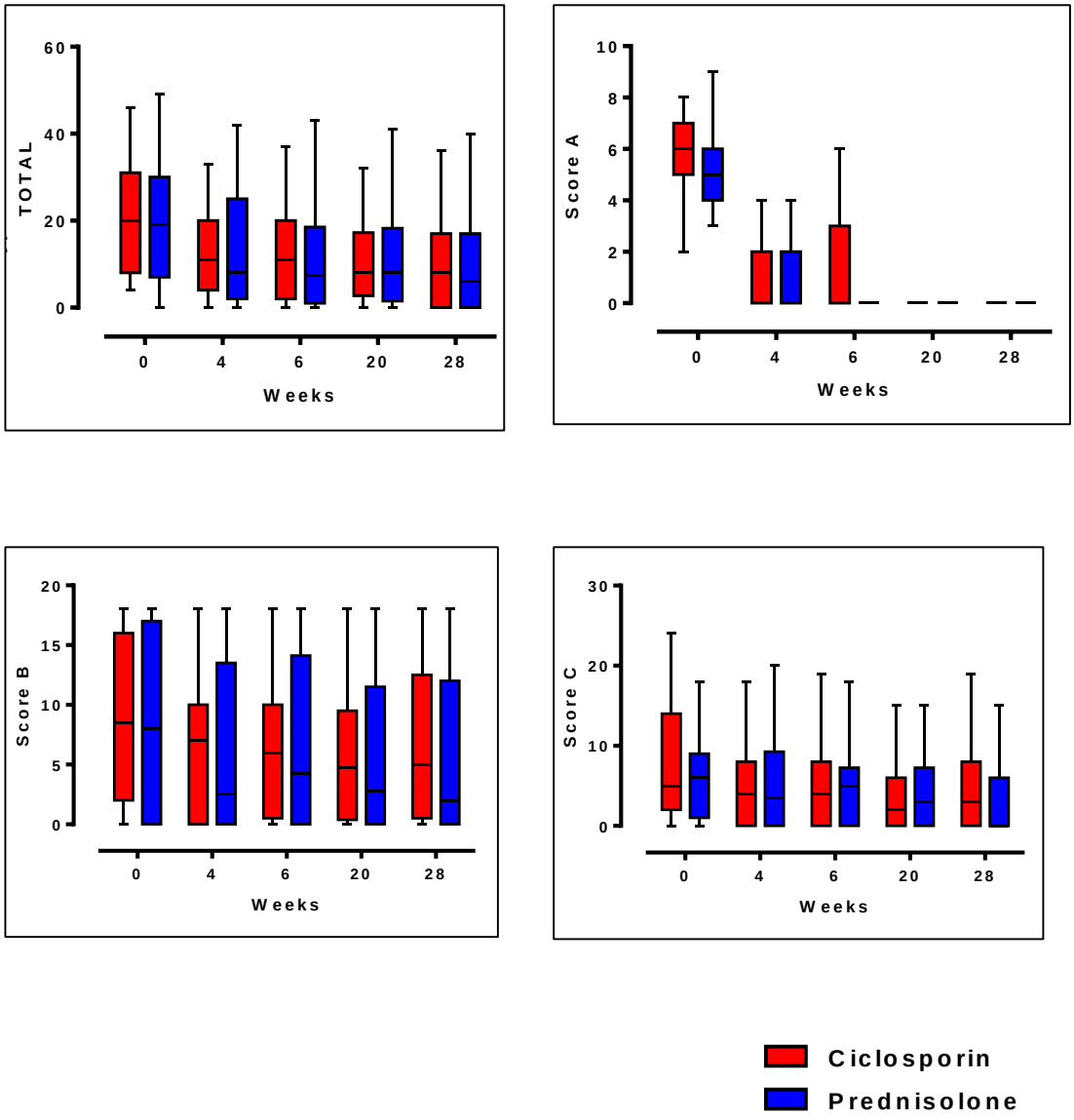


Figure 6.4 Median and inter-quartile ranges in clinical severity scores

All four components of the severity scores show a downward trend, suggesting improvement in both groups of patients. The largest and sustained decrease in score occurs in the skin (A) (Figure 6.5). At week 6, the difference in skin score between the two treatment arms is evident with the patients in the ciclosporin arm having a wider range in score despite a similar median score. Throughout the 32 weeks in the study, the median sensory score (B) does not reach the score of 0, which represents intact sensation. This may be due to nerves with old NFI producing higher scores which do not improve with time. This is also reflected in the Clinical Severity Score graph in which a median score of 0 is not achieved despite patients not showing any signs of acute reaction in the latter weeks of the study.

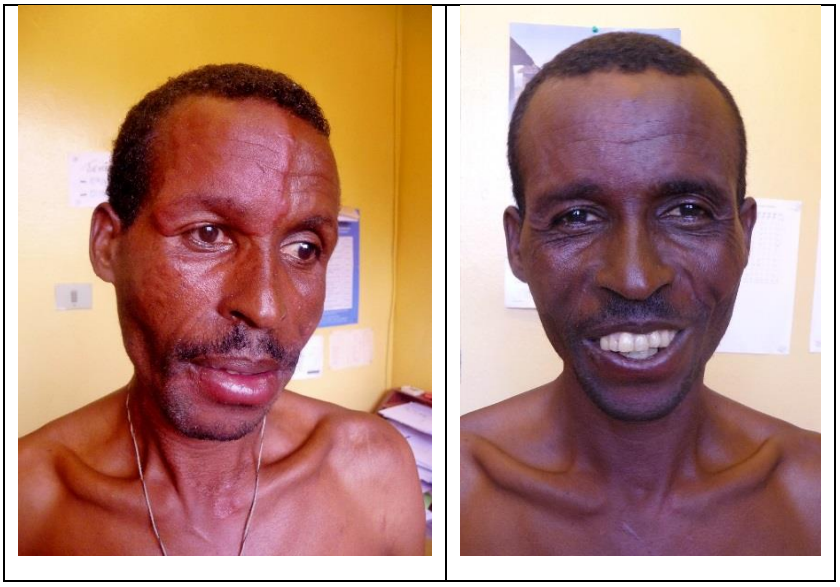


Figure 6.5 Man with facial T1R, on ciclosporin arm of study, before and after treatment

Analysis by patient and by nerves were also done to assess the improvement in T1R in patients treated with either ciclosporin or prednisolone. Table 6.5 shows the results of analysis by patient and Table 6.6 by nerves.

The general outcome for patients (Table 6.5) was decided by study physician assessment on review of patient notes and taking into account the changes in skin as well as nerves between week 0 and week 20, the end of the intervention period. There is no significant difference in all six clinical outcomes listed in Table 6.5 between the patients in the two treatment arms. Clinical outcomes in the follow-up period were recorded as those that maintained improvement and those that relapsed at the end of treatment. A larger proportion of patients appears to be maintaining improvement after the end of the intervention period in the ciclosporin arm (67% vs.39%, p=0.044).

Clinical outcomes in nerves (Table 6.6) at the end of treatment, week 20, were recorded as recovered, improved, not improved or worse (see section 3.1.3 for definitions). In the follow-up period between week 21 and 32, clinical outcome in the nerves were recorded as having remained stable or having had a relapse after treatment. Nerves were divided into those with new or old NFI as reported by patients at recruitment.

Clinical outcome in patients	Ciclosporin		Prednisolone		P value
Number of patients enrolled	35		38		
General T1R status					
No (%) recovered	1	**3%**	4	**11%**	
No (%) improved	31	**89%**	26	**75%**	0.254
No (%) not improved	3	**8%**	5	**14%**	
No (%) maintained improvement after Rx	*22*	***67%***	*12*	***39%***	*0.044*
No (%) relapsed after Rx	*11*	***33%***	*19*	***61%***	
Skin signs					
No (%) recovered	32	**91%**	31	**88%**	
No (%) improved	3	**9%**	2	**6%**	0.33
No (%) no change	0	**0**	2	**6%**	
No (%) maintained improvement after Rx	*28*	***85%***	*21*	***68%***	*0.143*
No (%) relapsed after Rx	*5*	***15%***	*10*	***32%***	
Sensation					
No (%) recovered	1	**3%**	0	**0**	
No (%) improved	22	**63%**	17	**49%**	0.204
No (%) no change (normal)	5	**14%**	12	**34%**	
No (%) not improved	7	**20%**	6	**17%**	
No (%) maintained improvement after Rx	*26*	***79%***	*23*	***74%***	*0.771*
No (%) relapsed after Rx	*7*	***21%***	*8*	***26%***	
Motor function					
No (%) recovered	16	**46%**	14	**40%**	
No (%) improved	10	**29%**	12	**34%**	0.957
No (%) no change (normal)	6	**17%**	6	**17%**	
No (%) not improved	3	**8%**	3	**8%**	
No (%) maintained improvement after Rx	*27*	***82%***	*29*	***94%***	*0.259*
No (%) relapsed after Rx	*6*	***18%***	*2*	***6%***	
Nerve tenderness					
No (%) improved	25	**71%**	22	**63%**	
No (%) no change (normal)	7	**20%**	12	**34%**	0.285
No (%) not improved	3	**9%**	1	**3%**	
No (%) maintained improvement after Rx	*28*	***85%***	*23*	***74%***	*0.359*
No (%) relapsed after Rx	*5*	***15%***	*8*	***26%***	
EHF Disability Score					
No (%) improved	23	**66%**	18	**51%**	
No (%) no change (normal)	9	**26%**	16	**46%**	0.168
No (%) worse	3	**8%**	1	**3%**	

T test done with Chi Square

Table 6.5 Clinical outcome in patients with acute T1R

Clinical outcome in nerves	Ciclosporin (n=35)		Prednisolone (n=38)		p value
Voluntary muscle testing (VMT)					
Number of nerves tested (n=876)	420		456		
Normal nerves	277	66%	289	63%	
No (%) not finished intervention/follow-up	24	6%	96	21%	
NERVES WITH NEW WEAKNESS	**116**	**28%**	**96**	**20%**	
No (%) recovered	76	66%	49	51%	0.085
No (%) improved	9	8%	17	17%	
No (%) not improved	14	12%	15	16%	
No (%) worse	17	14%	15	16%	
No (%) remained stable after Rx	*96*	*88%*	*76*	*76%*	*0.648**
No (%) relapsed after Rx	*13*	*12%*	*8*	*24%*	
NERVES WITH OLD WEAKNESS	**27**	**6%**	**23**	**5%**	
No (%) recovered	7	26%	5	22%	0.531
No (%) improved	3	11%	4	17%	
No (%) not improved	15	56%	14	61%	
No (%) worse	2	7%	0	0	
No (%) remained stable after Rx	*24*	*89%*	*14*	*100%*	*0.539**
No (%) relapsed after Rx	*3*	*11%*	*0*	*0*	
Sensory testing (ST)					
Number of nerves tested (n=438)	210		228		
Normal nerves	73	35%	95	42%	
No (%) not finished intervention/ follow-up	12	6%	48	21%	
NERVES WITH NEW SENSORY LOSS	**93**	**44%**	**56**	**25%**	
No (%) recovered	35	38%	19	35%	0.076
No (%) improved	30	32%	12	21%	
No (%) not improved	20	21%	12	21%	
No (%) worse	8	9%	13	23%	
No (%)remained stable after Rx	*68*	*78%*	*38*	*79%*	*1.000**
No (%) relapsed after Rx	*32*	*22%*	*10*	*21%*	
NERVES WITH OLD SENSORY LOSS	**44**	**21%**	**53**	**23%**	
No (%) recovered	5	12%	4	8%	0.688
No (%) improved	15	34%	15	28%	
No (%) not improved	23	52%	31	58%	
No (%) worse	1	2%	3	6%	
No (%)remained stable after Rx	*31*	*74%*	*42*	*82%*	*0.447**
No (%) relapsed after Rx	*11*	*26%*	*9*	*18%*	

*T test done with Chi Square except * (Fisher exact test)*

Table 6.6 Clinical outcome by nerves in patients with acute T1R

The change in motor function, between baseline and the end of intervention, in nerves with reported weakness of less than six months duration is not significantly different between the two study arms (p=0.085). Figure 6.6 illustrates that motor function in both treatment arms recovered or improved in a large proportion of nerves (74% in the ciclosporin arm and 68% in the prednisolone arm).

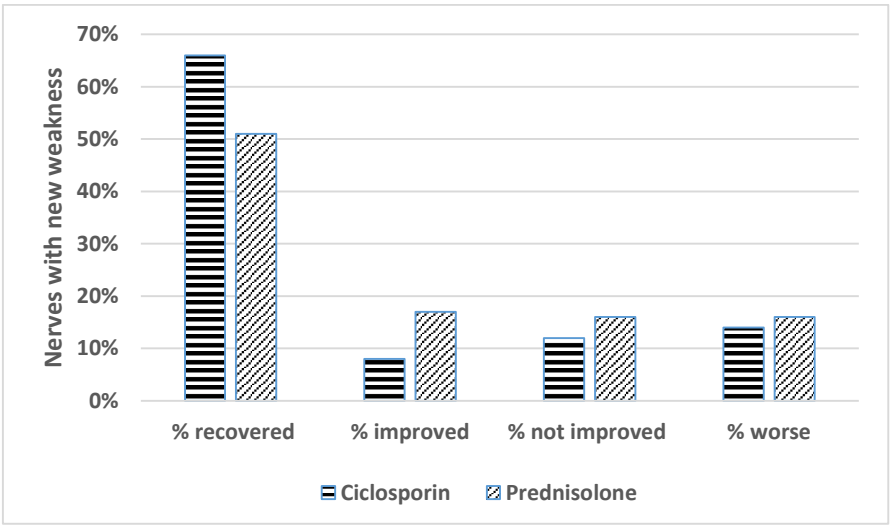


Figure 6.6 Motor function change in nerves with new weakness

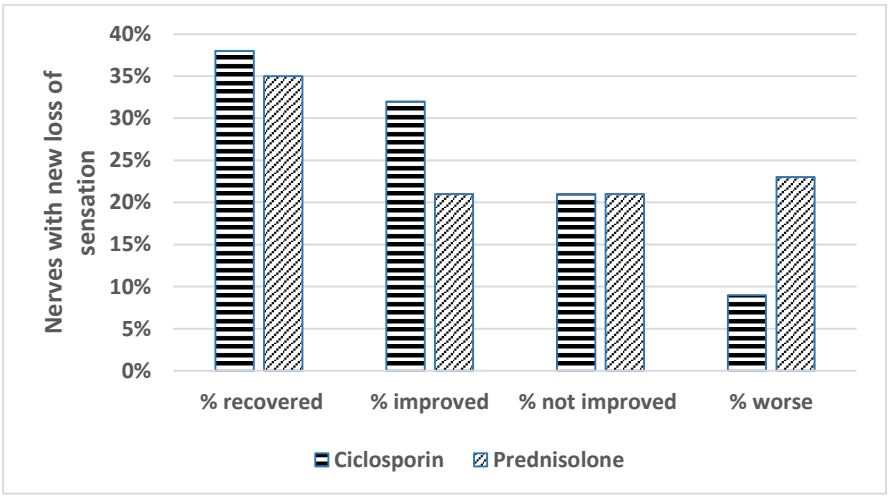


Figure 6.7 Sensory function change in nerves with new loss of sensation

70% of nerves with sensory loss reported as being of less than six months duration in the ciclosporin arm and 56% in the prednisolone arm improved or recovered (Figure 6.7). There was no statistically significant different in improvement of sensory function between the two treatment arms (p= 0.076).

Patients in both treatment arms had their nerves assessed three months after the end of the intervention and improvement in nerve function was maintained in the majority of patients. Motor function remained stable in 88% (Cn arm) and 76% (P arm), and sensory function in 78% (Cn arm) and 79% (P arm).

Nerves reported to have been impaired for longer than six months also showed improvement (Figure 6.8 and Figure 6.9).

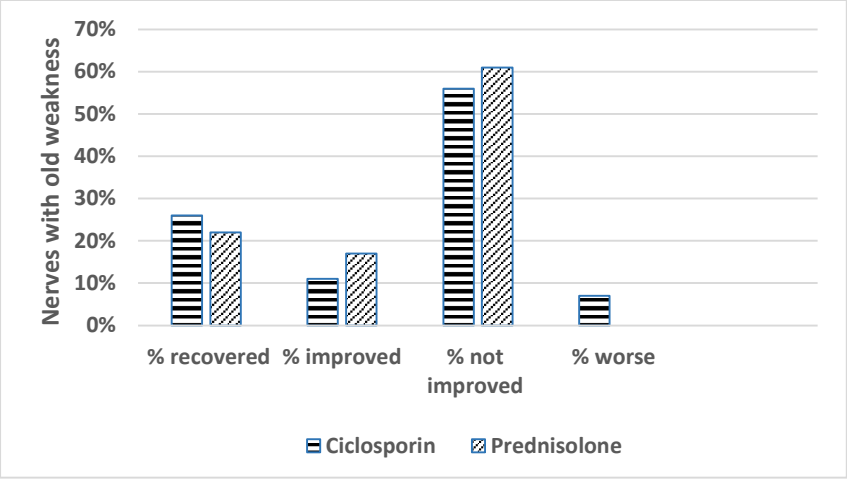


Figure 6.8 Motor function change in nerves with old weakness

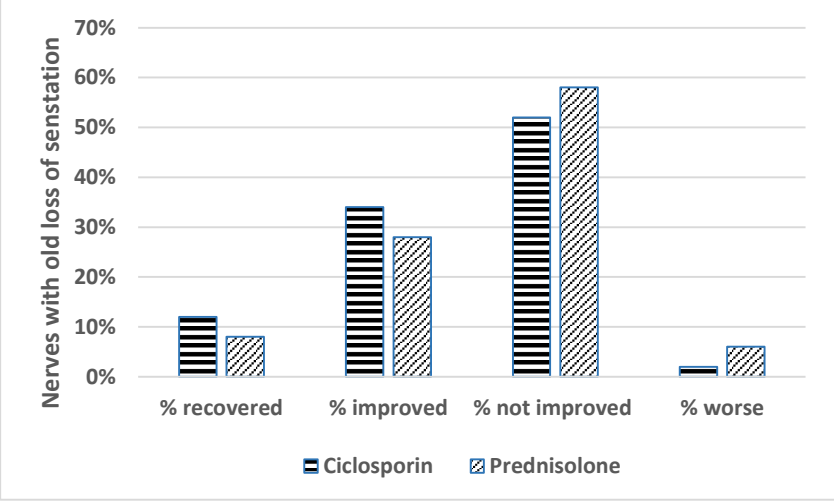


Figure 6.9 Sensory function change in nerves with old loss of sensation

6.1.3 Secondary outcomes

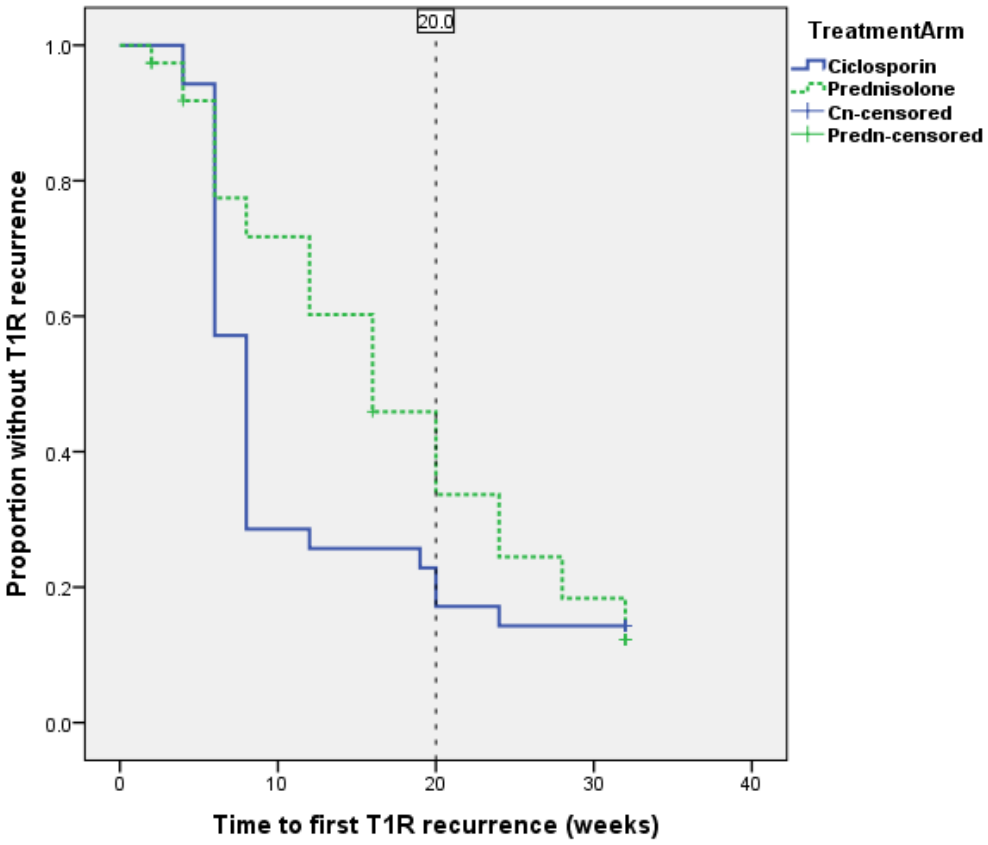
1. Mean time to recurrence of T1R

T1R recurrence after initial control was defined in section 3.1.3 as an increase in skin severity score to 4 or more out of 9 AND/OR an increase in NFI defined as worsening of VMT by one point in two or more muscles, or by 2 points in one muscle AND/OR worsening of ST: decreased sensation in at least two out of 3 points per nerve on the hand and/or 3 or more points on the feet, were required. NFI impairment is often accompanied by new nerve tenderness, but not necessarily. A T1R recurrence was treated with an increase in prednisolone, according to the protocol (see section 3.3.3).

Fifty nine out of 69 (85%) patients recruited with acute T1R had a T1R recurrence.
Of the 73 patients recruited to the study, the three who withdrew from the prednisolone arm early in the study, and one patient in the prednisolone arm who had ENL recurrences only throughout the 32 weeks in the study have been removed from this analysis. Ten patients had no T1R recurrence during the 32 weeks in the study: five patients in the ciclosporin arm and five in the prednisolone arm. Six patients, two in the ciclosporin arm and four in the prednisolone arm, had an ENL episode, in the 32 weeks in the study. These patients experienced both ENL and T1R, and so have been retained in the analysis.

The cumulative probability of T1R recurrence at a given point of time is shown on a Kaplan-Meier survival curve and there is no statistically significant difference between the two treatment arms (Log Rank- Mantel Cox, p= 0.157) (Figure 6.10).

The mean time to first episode of T1R recurrence was 8.7 weeks (median=8) in the ciclosporin group and 15.2 (median=16) weeks in the prednisolone group. The earlier time to first recurrence in the patients on the ciclosporin arm was statistically significant (Mann-Whitney U Test, p=0.0058).



Time point in weeks	0	4	6	8	12	16	20	32
Number at risk Cn arm	35	33	20	10	9	9	6	5
Number at risk Pred arm	37	32	27	25	21	15	11	5

**Week 20 line represents the end of study intervention*
Censored= patients lost to follow-up or removed from study
(Overall Median =12 weeks, 95%CI: 9.1-14.9)

Figure 6.10 Survival curve for patients without a T1R recurrence (T1RA)

Figure 6.11 shows a cluster of T1R recurrence events around week 6 and week 8 in the ciclosporin arm patients. The analysis of Clinical Severity Score showed that at weeks 6 and 8, there was a statistical significant difference between the two treatment arms on the skin related A score. Prednisolone was given for the first four weeks of the study to patients on the ciclosporin arm to cover for the slow onset of action of ciclosporin. At week 4 prednisolone is stopped in these patients and many of them are having a flare-up of T1R at weeks 6 and 8, in particular in the skin signs of T1R.

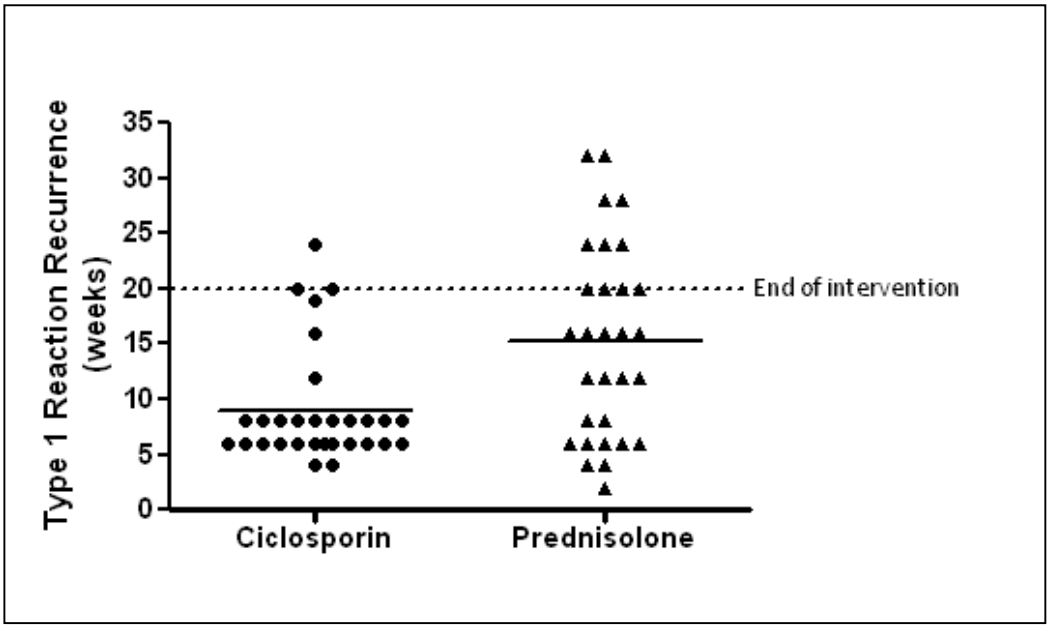


Figure 6.11 Time of first recurrence of T1R after initial control – T1RA

2. Number of T1R recurrence episodes

The mean number of recurrence per patient was 1.35 (median 1) for the patients in the ciclosporin arm and 1.49 (median 1) for the patients in the prednisolone arm. There was no statistically significant difference between the two arms (Mann-Whitney U Test p= 0.365).

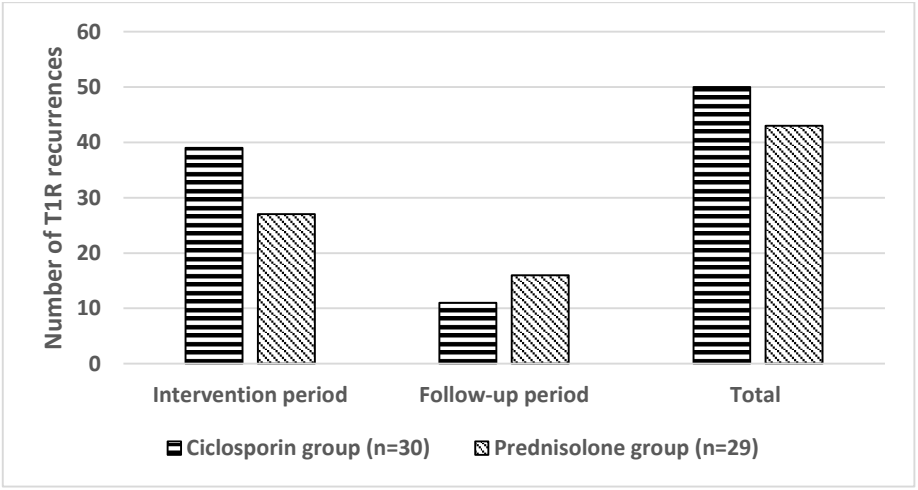


Figure 6.12 Number of T1R recurrence episodes per treatment arm in the intervention and follow-up periods

A total of 93 episodes of T1R recurrence were experienced by the 59 patients. The largest difference in numbers of T1R recurrences occurs during the intervention period, with patients in the ciclosporin group experiencing 13 more recurrences than those in the prednisolone group (Figure 6.12). The difference in numbers of T1R recurrences within the intervention period or the follow-up period were not statistically significant.

3. Severity of T1R

The severity of the 93 episodes of T1R recurrence was graded in two ways. Severity grading using the Clinical Severity Score (Figure 6.13) was compared to the physician's opinion on the severity, with the options of grading each T1R episode as none, mild, moderate or severe (Figure 6.14).

Patients in the ciclosporin arm had more T1R recurrences than those in the prednisolone arm during the treatment period. In both intervention and follow-up periods, there was no statistically significant difference in the distribution of severity of recurrences between the two treatment arms, when graded by the Clinical Severity Score (Chi Square p=0.926 and p=0.162 respectively) and the physician's opinion (Chi Square, p=0.653 and p=0.573 respectively).

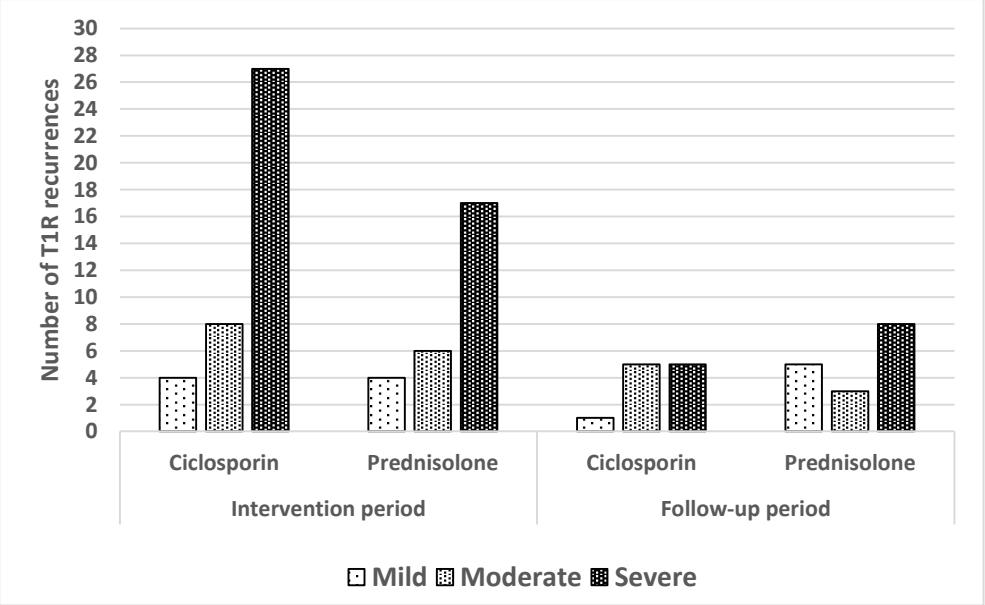


Figure 6.13 Number of T1R recurrence episodes by Clinical Severity Score

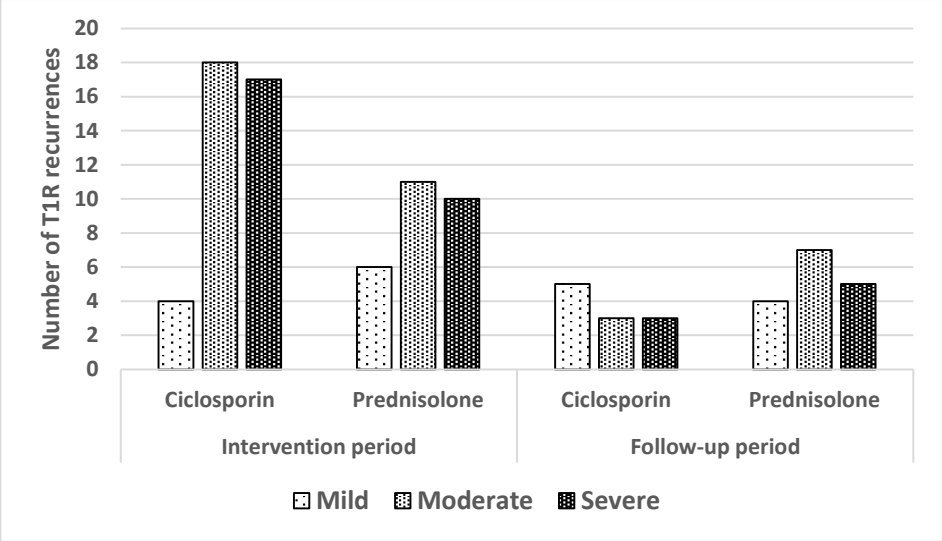


Figure 6.14 Number of T1R recurrence episodes by specialist severity grading

There is a large variation in the categorisation of T1R severity by the two methods, especially in the severe and moderate category. Physicians graded the T1R recurrence episodes more moderately than the Clinical Severity Score. One explanation for this may be that old and new NFI cannot be differentiated by the Clinical Severity Score.

4. Amount of extra prednisolone

Additional prednisolone for reaction flare-up was prescribed following the protocol in section 5.3.3. Table 6.7 shows the summary data for mean additional and total prednisolone received by all the patients recruited, per treatment arm.

Period in study	Ciclosporin arm (n=35)	Prednisolone arm (n=38)	Whole group (n=73)	P value (Mann Whitney U test)
INTERVENTION PERIOD	1608 (0-5705) 1400	559 (0-2030) 0	1062 (0-5705) 840	<0.000
FOLLOW-UP PERIOD	1067 (0-2870) 1260	799 (0-2310) 623	927 (0-2870) 980	0.208
TOTAL STUDY PERIOD	2680 (0-8085) 2520	1358 (0-3710) 1435	1992 (0- 8085) 1820	0.002
TOTAL PREDNISOLONE	3450 (770-8855) 3290	4208 (3010 -6160) 4445	3845 (560 -8855)	0.031

Table 6.7 Additional and total prednisolone received in patients in T1RA
(group mean, range and median in mg)

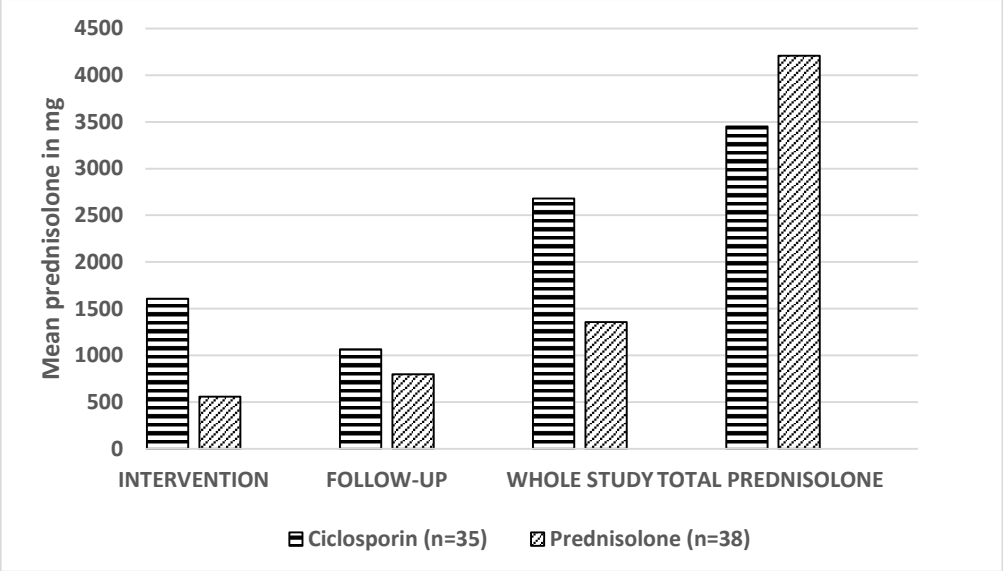


Figure 6.15 Additional and total prednisolone received in patients in T1RA

Patients in the ciclosporin arm received significantly more additional prednisolone during the intervention period ($p<0.000$) and in the total study period ($p=0.002$). Patients in the ciclosporin arm received 10% less steroid (mean 758mg) in total than the patients in the prednisolone arm (Figure 6.15).

Sixty patients in total received additional prednisolone during the study. Additional prednisolone was given for 91 T1R occurrences, as defined in the study protocol, and two for isolated nerve tenderness (Table 6.8). Twelve ENL episodes occurred in six patients during the study. Ten patients, five in each study arm did not require additional prednisolone.

Reason for extra prednisolone	Ciclosporin arm	Prednisolone arm
RR (skin involved)	24	16
Neuritis/ NFI	27	26
ENL	4	8

Table 6.8 Reasons for additional prednisolone

Excluding the patients with ENL does not alter the statistically significant differences seen in Table 6.7, in terms of additional prednisolone prescribed to each group.

In Table 6.9 the reaction recurrences are divided by severity and by their period of occurrence.

Type of Reaction		RR (n=40)		Neuritis/ NFI (54)		ENL (10)	
Study arm (number of episodes)		Cn (24)	Pred (16)	Cn (28)	Pred (26)	Cn (3)	Pred (7)
Severity of reaction	Mild	0	5	10	6	1	1
	Moderate	8	3	14	14	2	3
	Severe	16	8	4	6		3
Period of reaction recurrence	week 4-8	14	3	13	9	2	0
	week 12-20	7	6	7	8	0	1
	week 21-32	3	7	8	9	1	6

Table 6.9 Severity and timing of reaction flare-up needing additional prednisolone

The larger differences in frequency are highlighted in Table 6.9. Patients in the ciclosporin arm have more episodes of reaction recurrences requiring additional prednisolone. Severe recurrences involving skin flare-up (RR) are more frequent (16 vs 8) and occur more frequently in weeks 4 to 8 of the study.

An ANOVA was conducted to get a clearer impression on the difference of mean prednisolone required by patients in both treatment arms throughout the different weeks in the study (Figure 6.16).

There was a significant difference (p=0.003) in mean weekly prednisolone dose in both arms with time as less prednisolone was required by both groups as the study progressed. The week by week ANOVA breakdown shows the following important points:

- Weeks 4-15: significantly more prednisolone is taken by patients in the prednisolone arm
- Week 6: a sharp increase in prednisolone taken by patients on the ciclosporin arm is noted
- Week 20-24: significantly more prednisolone is taken by patients in the ciclosporin arm
- Week 24: an increase in the requirement of prednisolone is seen in patients on the prednisolone arm as flare-ups start to occur once the prednisolone regimen is stopped
- Week 29-32: at the end of the follow-up period, patients from the ciclosporin arm are on less prednisolone although this difference was not found to be statistically significant.

A large amount of additional prednisolone was given to patients on the ciclosporin arm, making it difficult to draw any conclusions about the benefits of ciclosporin alone.

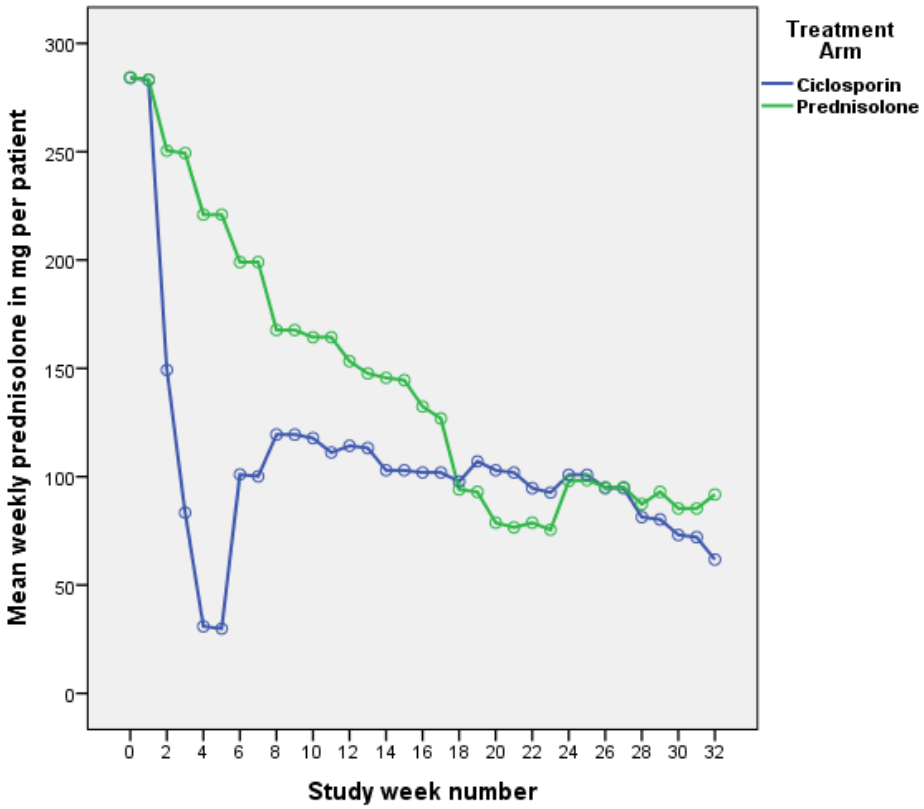


Figure 6.16 Weekly mean prednisolone per patient by treatment arm

5. Adverse Events

All the patients recruited to T1RA experienced at least one adverse event during their period in the study. Patients experiencing minor and/or major adverse events that may be attributed to the study drugs are shown in Table 6.10.

In Table 6.10, patients are listed according to the study arm they were assigned to regardless of any additional prednisolone received during the study period to control any recurrence in reaction symptoms. Patients who experienced blurred vision were referred to the ophthalmologist for ophthalmic review and had their serum glucose checked. Three patients in the ciclosporin arm developed anaemia approximately three months after starting MDT, and two patients had abnormal liver function tests

at week 4 which resolved spontaneously. Renal functions (measured by serum creatinine and urea) and potassium levels were stable for all patients except in the four patients who experienced a serious adverse event (see below).

DRUG RELATED ADVERSE EVENTS T1RA		Ciclosporin arm (n=35)	Prednisolone arm (n=38)
MINOR ADVERSE EVENTS	Moon Face	6	2
	Acne	10	13
	Fungal infections	10	8
	Gastric pain	19	14
MAJOR ADVERSE EVENTS	Infections	18	12
	Infected ulcers	14	14
	Hypertension	4	0
	Diabetes mellitus	1	1
	Nocturia	3	1
	GI bleeding	0	2
	Pulmonary tuberculosis	1	0
OTHER ADVERSE EVENTS	Headache	6	2
	Night sweats	3	3
	Hypertrichosis	1	0
	Gum hyperplasia	4	0
	Depression /anxiety	3	2
	Dysuria	2	0
	Vomiting	4	1
	Diarrhoea	3	5
	GI infection - bacterial	4	1
	GI infection - Giardia	3	4
	GI infection - H.pylori	2	4
	Blurred vision	2	3
	Conjunctivitis	3	3

Table 6.10 Number of patients experiencing minor and major adverse events *related to ciclosporin and/ or prednisolone (T1RA)*

		Ciclosporin (140)	Prednisolone (128)
Severity of adverse event	Mild	58	66
	Moderate	70	49
	Severe	12	13

Table 6.11 Number of adverse events classified by severity

Adverse events were also graded by severity, using the Common Terminology Criteria for Adverse Events (CTCAE, 2008) grading system. There was no significant difference (p=0.175) in the number of adverse events, classified by severity for each study arm (Table 6.11).

Table 6.12 lists the five serious adverse events which occurred in this study. Three were definitely attributable to prednisolone and one definitely to ciclosporin. The fifth case, a patient diagnose with pulmonary TB at week 22 (two weeks after stopping ciclosporin), may be attributable to both immune-suppressive drugs.

Results of routine blood laboratory, excluding the patients who had a severe adverse event, were remarkably stable throughout the 32 weeks of the study. Seven patients had a drop in haemoglobin by at least 2 g/dL during their time in the study. These patients had been started on MDT at the beginning of the trial and the haemoglobin drop was noted three months into the study. This is probably related to the dapsone in the MDT.

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Age/ Sex	Study arm	Event wk no	Adverse event	Grad -ing	Receiving pred	Pre-existing morbidity	Causality	Justification	Outcome
42/M	**Cn**	4	Severe headaches	3*	No	Severe headaches and visual blurring. Diagnosed with raised intra-cranial pressure.	Definitely related to ciclosporin	A rare but known side effect	Un-blinded. Ciclosporin stopped. Symptoms resolved. Continued on prednisolone
21/F	**Cn**	22	Pulmonary TB	4	Yes	Severe T1R necessitating high doses of additional prednisolone. Had 5705mg of additional prednisolone over 20 weeks	Definitely related to both drugs	Immuno-suppression caused by both ciclosporin and prednisolone	TB treatment given for 8 months No TB sequelae
58/M	**P**	2	Infective endophthal -mitis	4*	Yes	Severe T1R –hospital admission, noted to have conjunctivitis and corneal ulcer. Right eye infection unresponsive to topical and oral treatment, progressed to endophthalmitis.	Most probably related to prednisolone	Immuno-suppression may have led to progression of infection	Un-blinded, right eye e-nucleation, withdrew from study, continued on prednisolone at Health Centre
54/M	**P**	24	Death	5	Yes	Severe T1R, osteomyelitis, septicaemia and anaemia- all treated week 22. On additional prednisolone (2015mg over 24 weeks, total 5025mg) and proton pump inhibitor for severe dyspepsia.	Definitely related to prednisolone	Developed acute abdomen after severe dyspepsia. Possible perforated gastric ulcer and multi-organ failure	Death
24/M	**P**	26	Facial cellulitis	3	Yes	Dental abscess – progressed to facial cellulitis	Most probably related to prednisolone	Immuno-suppression	Recovered

Cn: ciclosporin arm; P: prednisolone arm, * Un-blinded

Grading: 1= Mild; 2= Moderate, 3= Severe; 4= Life-threatening or disabling; 5= Death (according to National Cancer Institute adverse event grading system –CTCAE)

Table 6.12 Serious adverse events in study T1RA

6. Quality of Life

Patients completed our validated SF-36 health related quality of life questionnaire in Amharic (see Chapter 7) at recruitment and at the end of the study. Each patient's quality of life is graded with two scores: a physical score (PCS) and a mental score (MCS), which in turn are composed of four subscales each. Of the initial 35 patients in the ciclosporin arm and the 38 in the prednisolone arm, 31 and 27 respectively completed the end of study questionnaire. No significant difference was detected between the changes in score for each study arm.

Table 6.13 shows the mean group score for each SF-36 scale at the start and at the end of the study, divided by treatment arm. The difference in group score between baseline and end of study is shown as the effect and the size of this effect is calculated and described following published standards. Roughly, standardised mean differences of less than 0.30 standard deviations are small effects, 0.30-0.80 are moderate, and more than 0.80 are large. All the scores were significantly increased ($p<0.05$) between the start and the end of the study except for the social functioning scale (SF) in both treatment arms. The changes in score in each scale, mostly with moderate and large effect size, are shown graphically in Figure 6.17. The largest score increase was in the bodily pain scale and the emotional role.

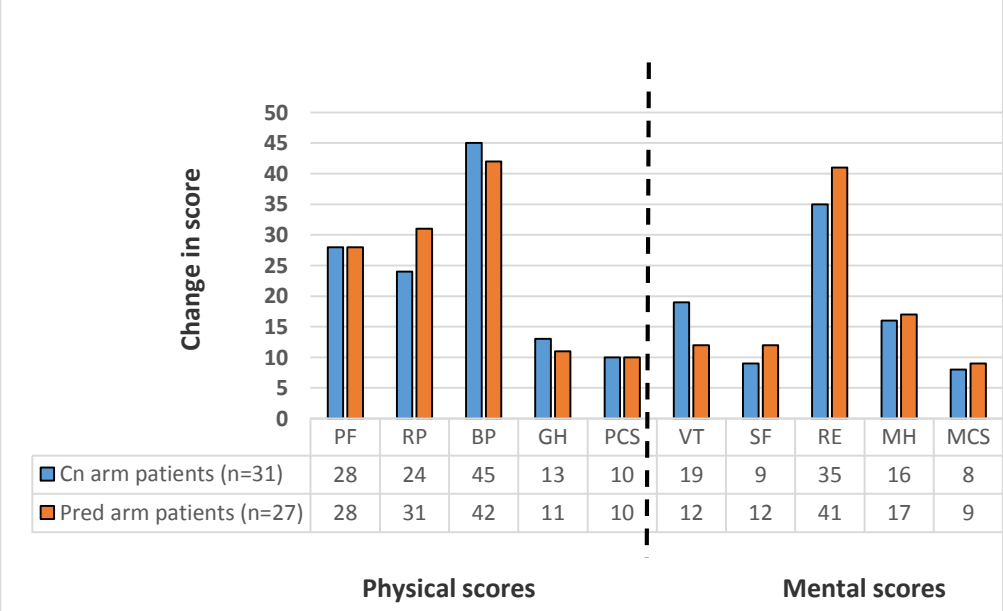


Figure 6.17 Change in SF-36 scores between start and end of T1RA study

Patients on Ciclosporin Arm

SF-36 variables T1RA	Baseline Mean ± SD	End of study Mean ± SD	Effect (Difference= end of study - baseline)			*p value* (paired sample t test)
			Mean ± SD	ES	ES description	
PF	50.8 ± 32.1	78.9 ± 20.3	28.1 ± 34.2	0.82	large	.000
RP	31.9 ± 27.2	55.8 ± 27.2	24 ± 36.3	0.66	moderate	.001
BP	20.5 ± 15.4	65.5 ± 30.7	45.1 ± 33.6	1.34	large	.000
GH	32.1 ± 18.8	45.3 ± 19.6	13.2 ± 23.4	0.56	moderate	.004
VT	38.1 ± 17.7	56.7 ± 20.4	18.5 ± 21.2	0.88	large	.000
SF	71.0 ± 37.0	80.2 ± 29.0	9.3 ± 38.6	0.24	small	.191
RE	28.0 ± 29.3	62.6 ± 32.8	34.7 ± 36.1	0.96	large	.000
MH	41.1 ± 22.7	57.4 ± 22.1	16.3 ± 27.1	0.6	moderate	.002
PCS	36.9 ± 7.2	47.4 ± 6.7	10.5 ± 9.8	1.06	large	.000
MCS	35.1 ± 10.3	43.2 ± 11.5	8.1 ± 11.9	0.68	moderate	.001

Patients on Prednisolone Arm

SF-36 variables T1RA	Baseline Mean ± SD	End of study Mean ± SD	Effect (Difference= end of study - baseline)			*p value* (paired sample t test)
			Mean ± SD	ES	ES description	
PF	54.3 ± 35.7	82.0 ± 20.1	27.8 ± 43.0	0.65	moderate	.002
RP	34.3 ± 31.6	64.8 ± 20.5	30.6 ± 38.7	0.79	moderate	.000
BP	28.9 ± 23.4	70.4 ± 25.6	41.5 ± 34.0	1.22	large	.000
GH	39.8 ± 18.6	50.3 ± 20.0	10.6 ± 21.2	0.5	moderate	.015
VT	48.8 ± 19.9	60.6 ± 19.1	11.8 ± 25.3	0.47	moderate	.023
SF	74.1 ± 33.2	85.6 ± 26.6	11.6 ± 41.6	0.28	small	.160
RE	33.3 ± 29.9	74.7 ± 22.2	41.4 ± 39.9	1.04	large	.000
MH	45.9 ± 21.7	63.3 ± 14.9	17.4 ± 22.8	0.76	moderate	.001
PCS	38.9 ± 9.8	48.6 ± 7.0	9.7 ± 12.5	0.78	moderate	.000
MCS	38.0 ± 10.4	47.0 ± 6.7	9.0 ± 10.2	0.88	large	.000

PF-physical functioning, RP-role physical, BP-bodily pain, GH-general health perceptions, VT-vitality, SF-social functioning, RE-role emotional, MH-mental health, PCS-physical component summary, MCS-mental component summary
SD= standard deviation;
ES= effect size= mean (effect)/ SD (baseline)

Table 6.13 Mean group SF-36 scores and the effect in score difference

6.1.4 Summary of findings for T1RA

Seventy three patients with newly diagnosed T1R were randomized to a 20-week intervention: treatment with either ciclosporin with prednisolone cover in the first four weeks or to prednisolone alone.

The two groups of patients had similar baseline characteristics and both groups showed a similar improvement in mean Clinical Severity Score as well as the three individual score components of skin, nerve sensation and motor function. Skin scores improved considerably in all patients but there was a statistically significant higher score in the ciclosporin group at weeks 6 and 8, suggesting skin flare-up around this time. During the treatment period, the recovery rate in skin signs was high with 91% of patients on the ciclosporin arm and 88% of patients in the prednisolone arm showing no signs of skin reaction at week 20.

Improvement in sensation was seen in nerves with recent onset sensory loss, with 70% of such nerves improving in the ciclosporin group and 56% in the prednisolone group. There was no significant difference between the two arms ($p=0.080$). Improvement in motor function was also seen in nerves with recent onset weakness, with 74% of these nerves in the ciclosporin group and 68% in the prednisolone group ($p=0.076$).

In the 12 weeks follow-up period, the motor function of 88% of affected nerves in the ciclosporin group and 76% in the prednisolone group remained stable, and the sensory function in 78% and 79% respectively remained stable. Nerve tenderness improved in most patients.

Old NFI, reported as having been present for longer than six months by patients at recruitment also showed improvement. Sensory function in these nerves improved in 46% and 36% in the ciclosporin and prednisolone arms respectively whilst motor function improved in 37% and 39% of affected nerves respectively.

Fifty nine patients (85%) had a T1R recurrence with similar numbers of patients in each treatment arm. Patients in the ciclosporin arm experienced a T1R recurrence eight weeks earlier than those in the prednisolone arm ($p=0.0058$). The mean number of T1R recurrences per patient was similar for both treatment arms, with more recurrences in the ciclosporin arms occurring during the weeks 0 to 20 intervention

period. The severity of these recurrences was not significantly different between the two treatment arms.

Patients in the ciclosporin arm received significantly more additional prednisolone during the intervention period than those in the prednisolone arm ($p<0.0001$). There is a sharp increase in the mean weekly requirements of additional prednisolone for the patients on the ciclosporin arm from week 6 onwards. Mean additional prednisolone received by the two groups during the 32 week study is significantly higher in the ciclosporin group (Cn 2680mg vs. P 1358mg, $p =0.002$). Mean total prednisolone received was of course significantly higher in the prednisolone arm (Cn 3450mg vs. P 4208mg, $p=0.031$) as patients in this arm were on a base regimen of prednisolone totalling 3080mg compared to the 770mg that patients in the ciclosporin arm received. There was only a 10% steroid-sparing effect in the patients on the ciclosporin arm.

The relatively subjective physician-determined outcome for general health status related to T1R improved in 94% of patients on the ciclosporin arm and 86% of patients in the prednisolone arm. A larger proportion of patients in the ciclosporin appeared to maintain that improvement (67% vs 39% with $p=0.044$) after the end of the intervention period. The EHF disability score improved in 66% of patients on the ciclosporin arm and 55% of patients on the prednisolone arm.

There were no significant difference in the frequency of either minor or major adverse events experienced by patients between the two treatment arms of the study.

The quality of life as measured by the eight SF-36 scales and the physical and mental summary components, improved significantly for patients with new T1R in both study arms. There was no significant difference between study arms.

6.2 RESULTS OF STUDY OF CICLOSPORIN IN CHRONIC T1R PATIENTS (STUDY T1RB)

A patient was diagnosed with chronic T1R, when he was developing new erythematous skin lesions or worsening neuritis despite steroid treatment or was not managing to remain free of T1R recurrence for at least four weeks without steroid.

6.2.1 Participants

Sixteen patients with chronic or recurrent T1R were enrolled into study T1RB between the 10th of August 2011 and 23rd of October 2012 (Figure 6.18).
Baseline characteristics for these patients are shown in Table 6.14. One patient in this group had PB leprosy, with one large facial patch.

Participants with chronic T1R	Ciclosporin (n=16)	
Sex	Women: men	7:9
Median age (years)	37	
Clinical Ridley- Jopling	TT BT BB BL LL PN	1 10 2 2 0 1
Mean of mean BI	at diagnosis at recruitment	1.2 0.2
MDT status	Started at enrolment Current Completed	0 4 12
Co-morbidities	2 hypertension 1 steroid induced glaucoma 1 median nerve decompression	
EHF score (mean)	3.56	

Table 6.14 Description of study participants in T1RB study

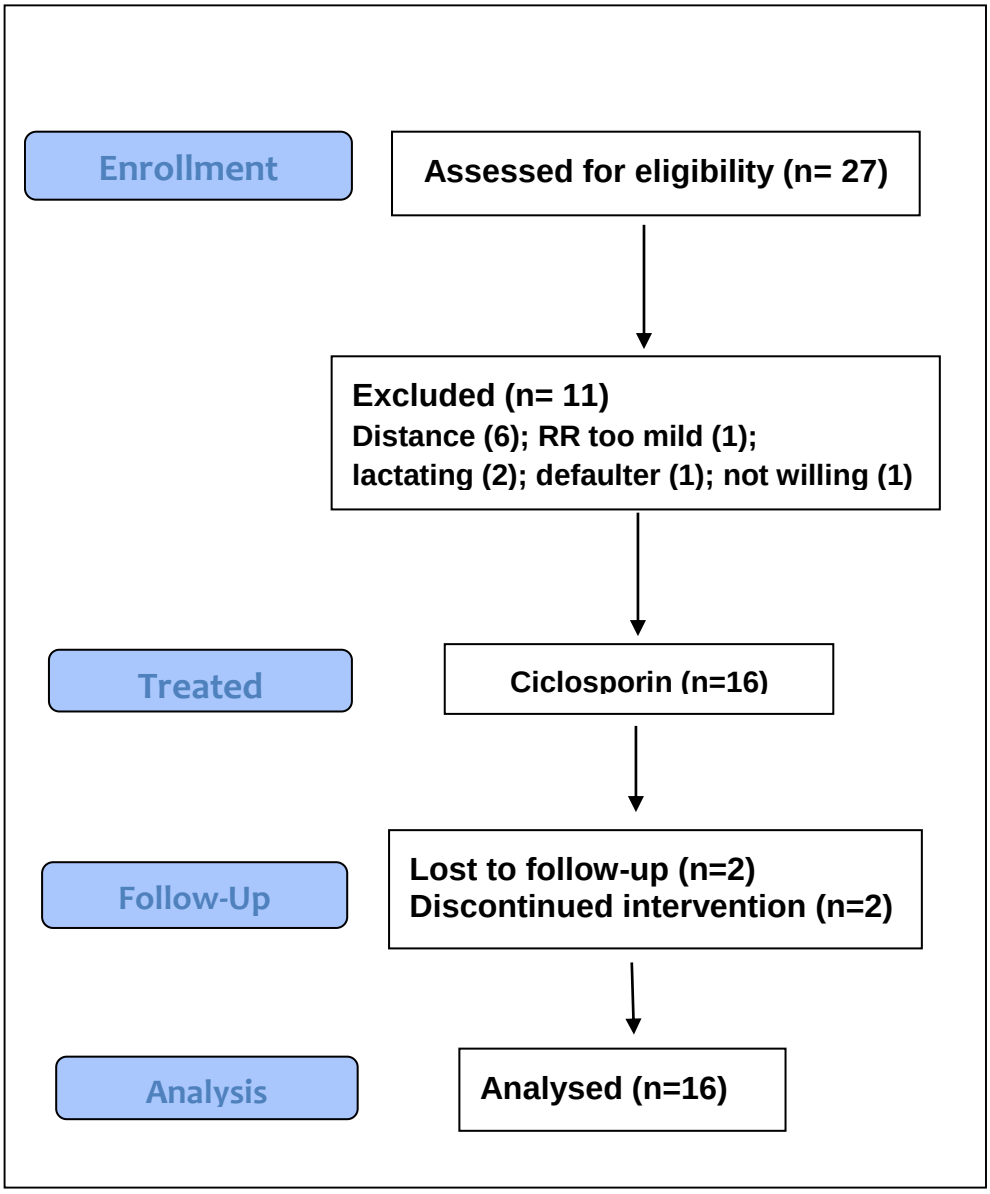


Figure 6.18 Flow diagram for T1RB study

Lost to follow-up

Two participants did not attend from week 2 and week 12 respectively. Ciclosporin was stopped in one participant following a serious adverse event in which she developed pulmonary TB at week 12. The fourth participant was removed from the study at week 8 for non-compliance with treatment.

Fifteen out of 16 participants had been on prednisolone for more than 12 months, and one patient had had five years of prednisolone treatment. The mean dose of prednisolone at recruitment was 13mg (range 0-40mg). The majority of patients had reaction in both skin and nerves with a median duration of active T1R of 21 days. All were graded as having severe reaction by the specialist who examined them (Table 6.15).

		Participants with chronic or recurrent T1R (n=16)
Reaction type	Skin only	2
	Skin and nerves	13
	Nerve only	1
Facial patches		14
Peripheral Oedema		12
Baseline NFI	None	4
	New	5
	Old	1
	Mixed old and new	6
Mean duration of T1R symptoms (days)		27 (7-60: median 21)
Median dose of prednisolone on recruitment		10mg (0-40)
Length of time on prednisolone (months)		6-60 (mean 26)
Severity by specialist opinion	Severe	16
Severity by Clinical Severity Score (mean)	Score A (skin)	5.06
	Score B (sensation)	7.44
	Score C (motor)	11.94
	Total CSS score	23.66

Table 6.15 Table showing reaction type and severity in patients with chronic T1R

Patients had a mean of 8.25 enlarged nerves and 4.75 tender nerves. 40% of nerves were tender with the ulnar, popliteal and posterior tibial nerves being most frequently affected. New NFI was present in 30% of nerves and sensory impairment was more prominent than motor impairment in both old and new NFI (Table 6.16).

Type of nerve involvement	192 nerves	
Type of new NFI	None	134 (70%)
	Sensory	32 (17%)
	Motor	15 (8%)
	Mixed	11 (5%)
Old NFI pattern	None	154 (80%)
	Sensory	19 (10%)
	Motor	3 (2%)
	Mixed	12 (6%)
Nerve tenderness		76 (40%)
Nerve enlargement		132 (69%)

Table 6.16 Nerve involvement in study participants with chronic T1R

6.2.2 Primary Outcome

Change in Clinical Severity Score and nerve function impairment

Figure 6.19 shows the changes in the group mean Clinical Severity Score over time for patients with chronic T1R on ciclosporin in comparison to those with acute T1R from study T1RA. Changes in the three sub-scores are also shown. The clinical response in the patients with chronic T1R, was similar to that in patients with new T1R. All 4 scores improved with time, although the skin score (A) showed the largest improvement.

Analysis by patient (Table 6.17) and by nerves (Table 6.18) were done to assess the improvement in T1R in patients treated with ciclosporin.

The general outcome for patients was decided by study physician assessment on review of patient notes and taking into account the changes in skin as well as nerves between week 0 and week 20, the end of the intervention period. Clinical outcomes in the follow-up period were recorded as those that maintained improvement and those that relapsed at the end of treatment.

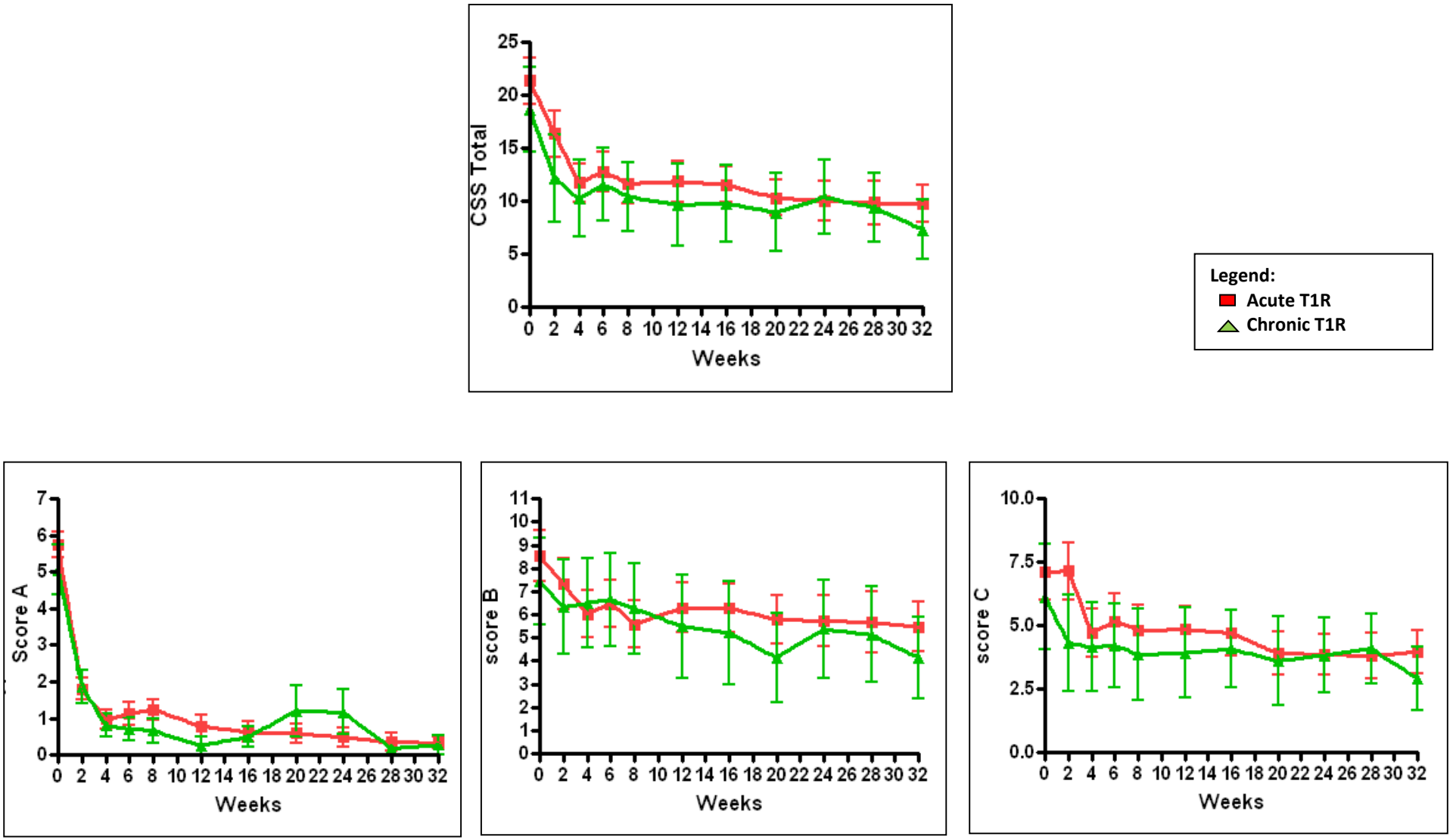


Fig 6.19 Group mean and standard error in Clinical Severity Scores for patients with acute and chronic T1R treated with ciclosporin for 20 weeks; with breakdown for Score A (skin), Score B (sensation) and Score C (motor).

Number of patients enrolled	16	
	Numbers	%age
General T1R status		
No (%) improved	13	**100%**
No (%) maintained improvement after Rx	*5*	**42%**
No (%) relapsed after Rx	*7*	**58%**
Skin signs		
No (%) recovered	7	**54%**
No (%) improved	6	**46%**
No (%) maintained improvement after Rx	*5*	**42%**
No (%) relapsed after Rx	*7*	**58%**
Sensation		
No (%) improved	3	**23%**
No (%) no change	4	**31%**
No (%) maintained improvement after Rx	*2*	***17%***
No (%) relapsed after Rx	*1*	***8%***
Motor function		
No (%) recovered	4	**31%**
No (%) improved	4	**31%**
No (%) no change	5	**38%**
No (%) maintained improvement after Rx	*11*	***92%***
No (%) relapsed after Rx	*1*	***8%***
Nerve tenderness		
No (%) improved	10	**77%**
No (%) no change	3	**23%**
No (%) maintained improvement after Rx	*11*	***92%***
No (%) relapsed after Rx	*1*	***8%***
EHF Disability Score		
No (%) improved	5	**42%**
No (%) no change	6	**50%**
No (%) worse	1	**8%**

Table 6.17 Clinical outcome in all patients with chronic T1R treated with ciclosporin

Patients showed a degree of improvement in all the clinical outcome measures.

Motor function recovered or improved in 78% of nerves. 63% of nerves with sensory loss, reported as being of less than six months duration, improved or recovered. Improvement was maintained in 89% of nerves, when tested 3 months after the end of the intervention (Table 6.18).

28% of motor nerves and 9% of sensory nerves reported to have been impaired for longer than six months also showed improvement.

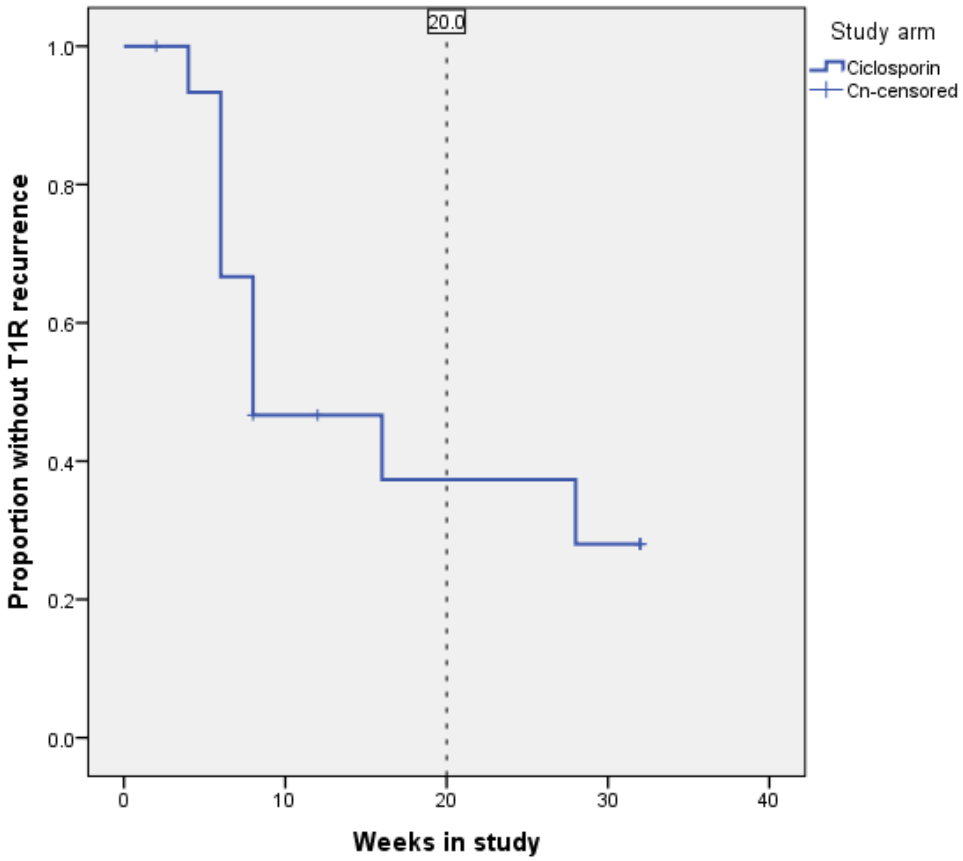
Number of patients with chronic T1R	16	
Voluntary muscle testing (VMT)		
Number of nerves tested	192	
Normal nerves	110	57%
No (%) not finished intervention	48	25%
NERVES WITH NEW WEAKNESS	**27**	**14%**
No (%) recovered	15	56%
No (%) improved	6	22%
No (%) not improved	**2**	7%
No (%) worse	4	15%
No (%) remained stable after Rx	*24*	*89%*
No (%) relapsed after Rx	*3*	*11%*
NERVES WITH OLD WEAKNESS	***7***	***4%***
No (%) recovered	*1*	14%
No (%) improved	1	14%
No (%) not improved	**5**	72%
No (%) remained stable after Rx	*6*	*86%*
No (%) relapsed after Rx	*1*	*14%*
Sensory testing (ST)		
Number of nerves tested	96	
Normal nerves	42	44%
No (%) not finished intervention	24	25%
NERVES WITH NEW SENSORY LOSS	**19**	**20%**
No (%) recovered	7	37%
No (%) improved	5	26%
No (%) not improved	7	37%
No (%) remained stable after Rx	*17*	*89%*
No (%) relapsed after Rx	*2*	*11%*
NERVES WITH OLD SENSORY LOSS	**11**	**11%**
No (%) recovered	0	0%
No (%) improved	1	9%
No (%) not improved	10	91%
No (%) remained stable after Rx	*11*	*100%*
No (%) relapsed after Rx	*0*	*0%*

Table 6.18 Clinical outcome by nerves in patients with chronic T1R

6.2.3 Secondary outcomes

1. Time to recurrence of T1R after initial control

Ten patients out of the 16 had a T1R recurrence. Two patients were lost to follow-up and one was withdrawn from the study at week 12 without having had a recurrence. Three patients completed the 32 weeks in the study without a T1R recurrence. This is illustrated in the Kaplan-Meier curve (Figure 6.20).



**Week 20 line represents the end of study intervention*

Figure 6.20 Survival curve for patients without a T1R recurrence (T1RB)

For the 13 patients who remained in the study up to end or to the first recurrence of T1R, the mean time to first recurrence of T1R is 9.1 weeks (median 8). A clustering effect around week 6 and 8 is seen as many of the recurrence occurred around this time (Figure 6.21).

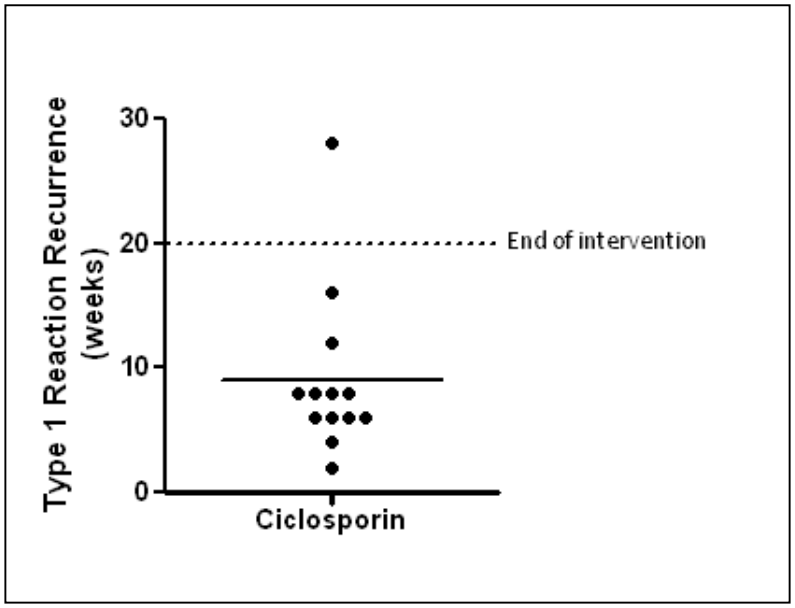


Figure 6.21 Time of first recurrence of T1R after initial control (T1RB)

2. Number of T1R recurrence episodes

For the ten out of 13 patients who experienced a T1R recurrence the mean number of recurrences per patient in this group is 1.21 (median 1, range 0 to 3). Nine episodes occurred during the intervention period and seven during the follow-up period.

3. Severity of T1R recurrence

The 16 episodes of T1R were graded for severity in two ways. Severity grading using the Clinical Severity Score (Figure 6.22) was compared to the physician's opinion on the severity, with the options of grading each T1R episode as none, mild, moderate or severe (Figure 6.23).

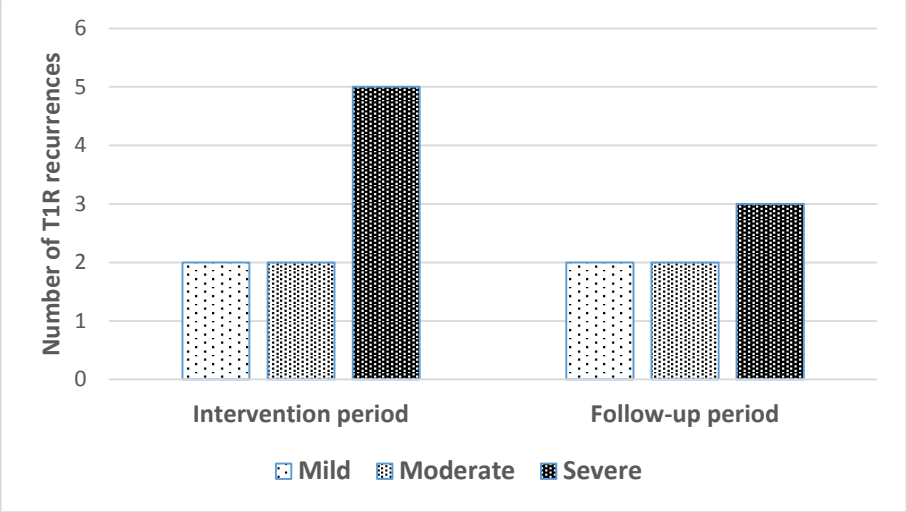


Figure 6.22 Number of T1R recurrence episodes by Clinical Severity Score

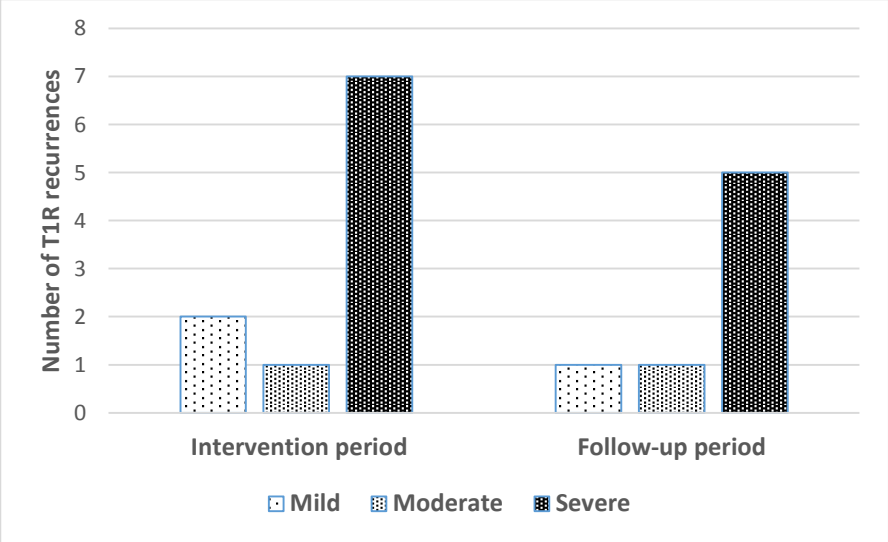


Figure 6.23 Number of T1R recurrence episodes by specialist severity grading

Both methods of grading gave similar distributions of severity grading between intervention and follow-up periods.

There is a large variation in the categorisation of T1R severity by the two methods, especially in the severe and moderate category. More T1R recurrences graded moderate by the Clinical Severity Score were graded as severe by physicians.

4. Amount of extra prednisolone

Table 4.19 shows the summary data for mean additional and total prednisolone prescribed to the patients. The reasons for additional prednisolone are ten episodes of skin and nerve reaction, six of nerve only reaction and one ENL.

Period in study	Additional prednisolone in mg; (n=16)
INTERVENTION PERIOD	1001, (0-3600), 670
FOLLOW-UP PERIOD	649, (0-2100), 490
TOTAL STUDY PERIOD	1629, (0-5390), 1295
TOTAL PREDNISOLONE	2290, (770-6160), 2030

Table 6.19 Additional and total prednisolone received in patients in T1RB
(group mean, range and median in mg)

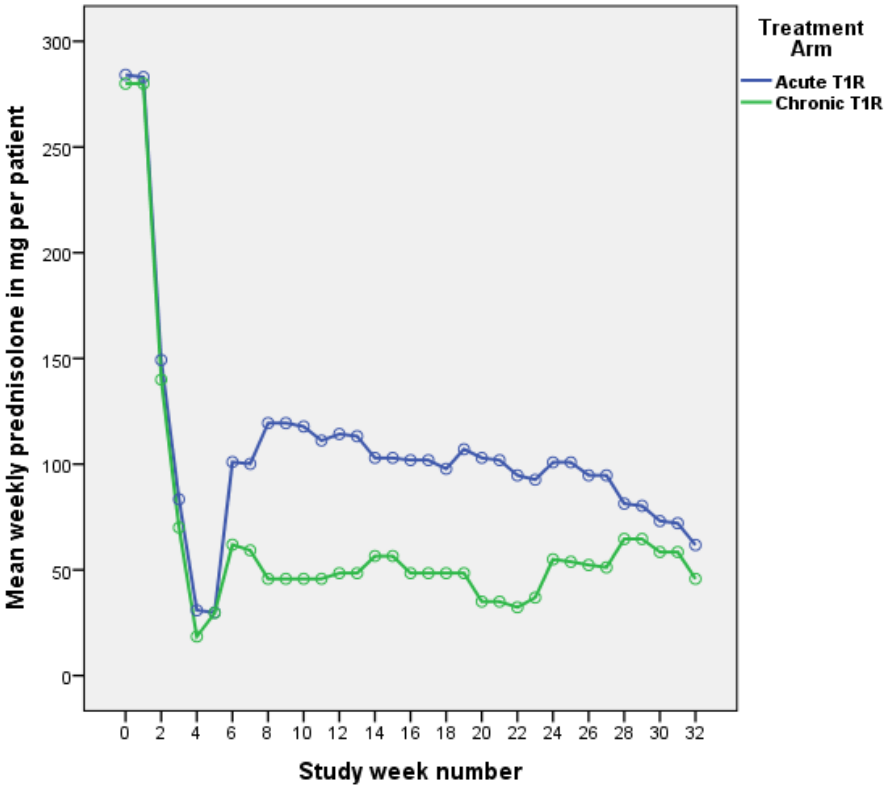


Figure 6.24 Weekly mean prednisolone per patient by treatment arm

Patients with chronic T1R required significantly less mean weekly prednisolone than patients with acute T1R throughout the study (ANOVA p=0.028) (Figure 6.24).

5. Adverse Events

Of the 16 patients recruited to study T1RB, 13 were prescribed additional prednisolone at some point during the 32 weeks, to control a flare-up in reaction. The number of patients who experienced drug related adverse events are shown in Table 6.20**.** All the patients in this study had previously received prednisolone and some had experienced prednisolone related adverse events prior to recruitment.

DRUG RELATED ADVERSE EVENT T1RB		Ciclosporin (n=16)	
		Present at recruitment	Developed during study period
MINOR ADVERSE EVENTS	Moon Face	2	3
	Acne	3	2
	Fungal infections	1	10
	Gastric pain	3	7
MAJOR ADVERSE EVENTS	Infections	1	10
	Infected ulcers	1	3
	Hypertension	0	4
	Nocturia	2	3
	Tuberculosis	0	1
OTHER ADVERSE EVENTS	Night sweats	1	0
	Hypertrichosis	0	4
	Gum hyperplasia	0	1
	Depression /anxiety		
	Dysuria	0	1
	Diarrhoea	1	4
	GI infection - bacterial	0	1
	GI infection - H.pylori	0	3
	Glaucoma	1	0
	Conjunctivitis	1	0

Table 6.20 Number of patients experiencing minor and major adverse events

One severe adverse event was recorded. Smear positive pulmonary TB was diagnosed in a 29 years old woman with severe ulcerating T1R. At recruitment, with

a history of 13 months of previous prednisolone usage, she was screened for TB. Sputum microscopy was negative for AFB and the chest X-ray was reported as normal. She developed cough and fever after 6 weeks of treatment with ciclosporin and prednisolone. Abundant AFB were found on repeat sputum microscopy. She started on rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE) therapy but developed drug induced hepatitis and all medication was either decreased or stopped. TB therapy was changed to ethambutol, isoniazid and streptomycin. Ciclosporin was later stopped at week 12, as she wanted to return to a hospital nearer to her family. Her reaction treatment was changed to prednisolone only and she was discharged with a stable VMT/ST with NFI but no nerve tenderness and no signs of skin RR.

6. Quality of Life

Patients completed our validated SF-36 health related quality of life questionnaire in Amharic at recruitment and at the end of the study. Of the 16 patients recruited, 11 had completed the end of study questionnaire. Seven patients improved in both physical and mental summary components and two had a lower score in both. Two more patients had an improvement in the physical component but a deterioration in the mental component.

Baseline physical and mental component summary scores are lower for patients with chronic T1R than those with acute T1R.

Table 6.21 shows the mean group score for each SF-36 scale at the start and at the end of the study. There is statistically significant increase ($p<0.05$) in the scales of PF, BP, RE, MH and the physical component summary scale. There are more score changes with small effect size in this group that in that of patients with acute T1R treated with ciclosporin.

The difference in change in score between patients with acute and chronic T1R for each SF-36 scale is shown graphically in Figure 6.25. For patients with both acute and chronic T1R, the largest change in score is in the bodily pain scale (BP) followed by the physical functioning scale (PF). The changes in quality of life scores are generally lower for patients with chronic T1R, except for the scales of social functioning (SF) and physical functioning (PF).

Ciclosporin T1RB (n=11)

SF-36 variables T1RB	Baseline Mean ± SD	End of study Mean ± SD	Effect (Difference= end of study - baseline)			*p value* (paired sample t test)
			Mean ± SD	ES	ES description	
PF	38.2 ± 29.7	70.0 ± 23.8	31.8 ± 29.3	0.83	large	.005
RP	32.4 ± 31.2	50.0 ± 21.5	17.6 ± 36.9	0.54	moderate	.144
BP	23.3 ± 11.7	59.2 ± 38.7	35.9 ± 42.0	1.54	large	.018
GH	38.4 ± 21.4	43.4 ± 22.4	5.0 ± 16.4	0.13	small	.337
VT	36.6 ± 17.0	62.5 ± 41.8	8.9 ± 25.1	0.24	small	.267
SF	79.5 ± 36.8	45.5 ± 21.2	17.0 ± 47.9	0.21	small	.265
RE	22.7 ± 27.7	56.1 ± 22.7	33.3 ± 33.7	1.47	large	.008
MH	36.4 ± 15.7	51.8 ± 16.8	15.5 ± 18.9	0.43	moderate	.022
PCS	36.9 ± 7.7	45.2 ± 8.2	8.3 ± 10.5	0.22	small	.025
MCS	34.6 ± 12.0	38.7 ± 9.4	4.1 ± 9.5	0.12	small	.184

PF-physical functioning, RP-role physical, BP-bodily pain, GH-general health perceptions, VT-vitality, SF-social functioning, RE-role emotional, MH-mental health, PCS-physical component summary, MCS-mental component summary
SD= standard deviation; ES= effect size= mean (effect)/ SD (baseline)

Table 6.21 Mean group scores and the effect in difference in scores for study T1RB

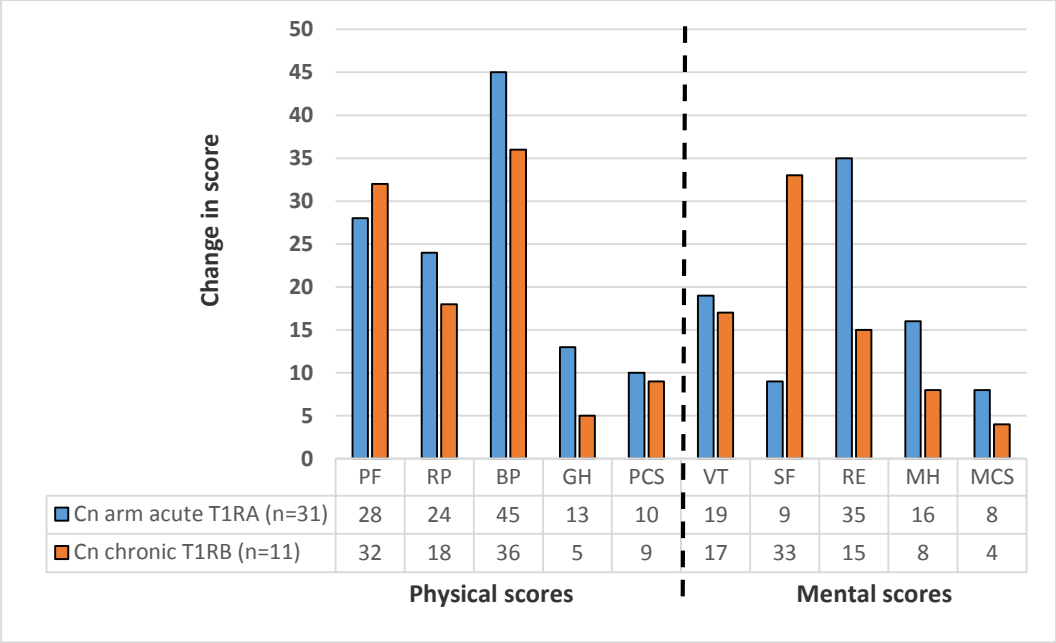


Figure 6.25 Change in SF-36 scores between start and end of study T1RB

6.2.4 Summary of findings for T1RB

Patients with chronic T1R showed good improvement in nerve function and skin inflammation with ciclosporin given for 20 weeks. The improvement in Clinical Severity Score in these patients was similar to that of patients with acute T1R treated with ciclosporin.

Skin signs improved in 100% of patients although 58% experienced a relapse after the end of treatment. Improvement in sensation was observed in 63% of nerves with recent onset sensory loss, and improvement in motor function was observed in 78% of nerves with recent onset motor function loss. Over 85% of nerves remained stable three months after the end of treatment.

Median time to first recurrence of T1R was 8 weeks and mean number of recurrences per patients was 1.21. These results are similar to those in patients with acute T1R treated with ciclosporin. The severity of T1R recurrence episodes were similar in the intervention and follow-up periods.

Mean additional prednisolone prescribed in patients with chronic T1R during the 32 weeks in the study was 1629mg, which is 1051mg less than that prescribed to patients on ciclosporin with acute T1R.

The rates of adverse events were also similar although patients with chronic T1R had been on long periods of prednisolone prior to recruitment and many had reported adverse events attributable to prednisolone at recruitment.

Quality of life scores in patients with chronic T1R improved in all the scales of SF-36 between the start and end of the study, although less than for patients with acute T1R.

6.3 DISCUSSION OF CICLOSPORIN IN T1R STUDIES

1. Clinical outcomes

Ciclosporin, a potent immunosuppressant, was described in three case reports as being an effective treatment for severe and recurrent T1R (Chin *et al.*, 1994; Frankel *et al.*, 1992). The pilot study carried out by the LSHTM group further assessed ciclosporin in 33 Ethiopian and eight Nepali patients with severe T1R (Marlowe *et al.*, 2007). A dose of ciclosporin in the range of 5-7.5mg/kg/day led to improvements in skin lesions in 85% of patients, nerve pain and tenderness in 45% of patients, sensory nerve impairment in 42% of patients and motor function in 53% of patients. Additional ciclosporin was prescribed when a deterioration in nerve function or skin lesions occurred. A direct comparison with prednisolone was essential as the next step in assessing efficacy of ciclosporin for T1R.

Our sample calculation was based on the Hypothesis of Non-Inferiority. A sample size of 48 patients per treatment arm was calculated with the assumption that prednisolone, based on previous studies discussed in the literature review, leads to an improvement of about 60% in nerve function in patients with new T1R. The non-inferiority margin of 0.25% was selected. Our study recruited a total of 73 patients, 35 in the ciclosporin arm and 38 in the prednisolone arm. This smaller sample size reduces the power to detect a significant difference in the study from 80% to 70%.

At the end of the 20-week intervention, both groups of patients showed an improvement in clinical outcomes as assessed by the physician. In patients receiving ciclosporin and prednisolone 100% of skin lesions had recovered or improved, 75% of motor nerves had improved or recovered, and 66% of sensory nerves had improved or recovered. In comparison, for patients receiving prednisolone only, the results showed that 94% of skin lesions had recovered, 74% of motor nerves had improved or recovered, and 49% of sensory nerves had improved or recovered. In patients with newly diagnosed T1R, both groups of patients recruited to either the ciclosporin and prednisolone arm or the prednisolone only arm had similar improvement rates in T1R severity as assessed by the Clinical Severity Score.

Skin lesions in patients on the ciclosporin and prednisolone arm flared up around weeks 6 and 8 of the study, just after the prednisolone cover was stopped at week 4. This suggests that the therapeutic level for ciclosporin had not been reached when the prednisolone was stopped. In the design of the study, the drug regimen for the ciclosporin study arm, assumed that four weeks of initial prednisolone would adequately cover the slow onset of action of ciclosporin. A number of problems can be identified in retrospect with this regimen. The onset of action of ciclosporin is reported to be between four to eight weeks (Sandoz., 1997), so potentially stopping the adjunctive prednisolone at week 4 was too early. Continuing prednisolone cover a bit longer may have prevented these early flare-ups in patients on ciclosporin.

Patients in the ciclosporin arm had fewer flare-ups in skin reaction signs during the follow-up period. This may be explained by the fact that the dose of prednisolone in these patients was higher in the early follow-up period as a result of additional prednisolone given for earlier flare-ups and therefore providing an extended protective effect. Patients in the prednisolone only group tended to have flare-ups in skin lesions towards the end of the intervention period and in the follow-up period as the dose of prednisolone was decreased or stopped.

In patients in both study arms, nerves reported to have been impaired for less than 6 months showed a good improvement rate in motor function (Cn 74% and P 68%) and in sensory function (Cn 70% and P 56%). Patients who received ciclosporin and prednisolone had better improvement in nerve function impairment than those who received prednisolone only (one tailed t test: motor function, p=0.043 and sensory function p=0.038). Improvement in nerve function in patients on the prednisolone only arm are similar to those reported in previous studies. In an open Bangladeshi study (n=132), it was reported that 68% of sensory nerves and 67% of motor nerves showed improvement after a 16-week course of prednisolone (Croft *et al.*, 2000). The small azathioprine study in Nepal showed that in patients in T1R (n=19) on prednisolone, only 60% had an improvement in VMT and 53% in ST (Marlowe *et al.*, 2004). In the methylprednisolone trial, 70% of the patients with T1R (n=42) who completed a 16 weeks course of prednisolone showed improved nerve function (Walker *et al.*, 2011).

Similar to previous studies, an important 24 to 32% of nerves did not improve with treatment. It may be that a proportion of these nerves with no improvement had been

affected for longer than six months or that the poor response to treatment may be due to physiological factors.

Between 36% and 46% of nerves that patients reported as having been affected for longer than six months improved in both sensory and motor function. Evidence for the six-month cut-off often used in deciding whether nerve function impairment should be treated with steroids is based on one TRIPOD study only (Richardus *et al.*, 2003b). There are huge problems in bias and patients' accuracy of recall with regards to the length of time the NFI has been present. Most of the patients in the new T1R study had not been diagnosed or not been previously seen at ALERT clinic, so that no previous VMT/ST assessments were available for comparison and dating of NFI. It is also difficult for patients to be exact about timing of sensory and motor NFI, especially when subtle changes can go unnoticed.

Patients with chronic T1R who received ciclosporin showed similar results for nerve function and skin lesion improvement to those of patients with new T1R treated with ciclosporin.

The timing of the first episode of T1R recurrence was significantly earlier for both acute and chronic T1R patients on ciclosporin (median 8 weeks) than those on the prednisolone only (median 16 weeks). This reflects the earlier mentioned increase in skin reaction a week or two after the prednisolone cover is stopped in the patients on ciclosporin. The mean and median number of recurrences per patient was not significantly different between patients on the two study arms. More T1R recurrence episodes occurred in the intervention period in the patients on ciclosporin but the severity of these recurrence was not significantly different from patients on prednisolone only.

Ten patients with acute T1R, five in each arm of the study, and three patients with chronic T1R had no T1R recurrence throughout the 32 weeks in the study.

2. Additional prednisolone

In the acute T1R study, 85% of patients had a T1R recurrence. The proportion of patients with T1R recurrence was similar for both study arms. This is a very high recurrence rate. In the Marlowe study, patients treated with ciclosporin had a recurrence rate of 50% in skin lesions, 71 % in sensory nerve impairment and 67% in

motor impairment (Marlowe *et al.*, 2007). In TRIPOD 2 (van Brakel *et al.*, 2003), 27% of patients with mild sensory impairment treated with prednisolone experienced deterioration necessitating additional prednisolone. In the Methylprednisolone study, 45% of patients on methylprednisolone and 50% of patients on prednisolone only required additional prednisolone for either skin or nerve deterioration (Walker *et al.*, 2011). In the Indian RCT looking at three different prednisolone regimens, the proportions of individuals with T1R or NFI of less than three months duration requiring additional prednisolone in the three groups was 24%, 31%, and 46% respectively. Individuals who received prednisolone for five months were significantly less likely to require additional prednisolone (Rao *et al.*, 2006). It is difficult to know whether the higher rate of recurrences in our study may be due to difference between Ethiopian and Indian or Nepalese patients, but the Marlowe study on ciclosporin which compared two groups did find that Ethiopians patients had a higher rate of T1R relapse compared to Nepalese patients (Marlowe *et al.*, 2007).

Significantly more additional prednisolone was required by patients in the ciclosporin arm both during the intervention period and the full 32 weeks of the study. Mean total weekly prednisolone received by patients on the ciclosporin arm was lower than that received by patients on the prednisolone arm throughout the study except for the period week 18 to 25. In total, the ciclosporin group received 10% less total prednisolone (p=0.031). The magnitude of this steroid sparing effect does not seem important enough to give a patient with T1R a 20-week course of an additional immune-suppressive drug such as ciclosporin unless a large difference in improvement of nerve function or in the rate adverse events is noted between the two treatment groups.

Patients with chronic T1R required significantly less additional prednisolone that patients with acute T1R (p=0.028) throughout the study. A direct comparison between ciclosporin and prednisolone for patients with chronic T1R would have given a more accurate picture as it difficult to assess how much prednisolone would be required to control symptoms of T1R in these patients. We could assume that patients with chronic T1R would have received a standard 20-week regimen of prednisolone (3080mg) when presenting with a flare-up. This assumption does not take into account additional prednisolone for flare-ups. If so, then patients with chronic T1R on ciclosporin, received a mean of 2290mg of prednisolone in total,

only a 14.7% reduction from the standard regimen. This difference could be even less, when correcting for the above assumption, as many patients with chronic T1R, usually get very small increments of prednisolone for flare-ups and not a full course of prednisolone starting at 40mg.

3. Adverse events

Adverse events in T1RA (Table 6.10) and T1RB (Table 6.20) were categorized by study arm. In these studies, as patients in the ciclosporin arm receive 4 weeks of prednisolone at the start of the study, and further prednisolone for any flare-ups of reaction, it is misleading too associate the adverse event entirely with ciclosporin.

To address this and refine the adverse events association with either prednisolone or ciclosporin, data in Table 6.10 and Table 6.20, were revised. Some adverse events are clearly related to one drug only, for example moon face and prednisolone, or gum hyperplasia and ciclosporin; other adverse events can be caused by either drug. When the adverse event occurred after the end of ciclosporin treatment (week 21), it was attributed to prednisolone if the patient was on additional prednisolone. Adverse events occurring, in the ciclosporin arm, at a time when patients were receiving high doses of additional prednisolone were attributed to prednisolone. Any equivocal adverse events that can be related to both drugs were separated out (Table 6.22). For patients with chronic or recurrent T1R, who would have been on long-term prednisolone prior to recruitment any side-effects identified at baseline were excluded. This exercise was done by three physicians independently, who then discussed any cases on which the judgement differed.

Table 6.22 suggests a higher rate of adverse events related to prednisolone than to ciclosporin. Pooling all four studies together gives a more accurate result for the frequency of adverse events attributable to either of the two medication. This is done in Chapter 8.

Serious adverse events which occurred in these studies, such as tuberculosis, diabetes and peptic ulcer perforation were linked to prednisolone.

DRUG RELATED ADVERSE EVENT T1RA and T1RB		Ciclosporin related	Equivocal	Prednisolone related
MINOR ADVERSE EVENTS	Moon Face	0	0	11
	Acne	2	9	14
	Fungal infections	3	8	17
	Gastric pain	5	7	28
MAJOR ADVERSE EVENTS	Infections	7	5	31
	Infected ulcers	4	12	40
	Hypertension	6	2	0
	Diabetes	0	1	1
	Nocturia	2	1	4
	GI bleeding	0	0	2
	Tuberculosis	0	2	0
OTHER ADVERSE EVENTS	Headache	5	0	3
	Night sweats	3	0	3
	Hypertrichosis	5	0	0
	Gum hyperplasia	5	0	0
	Depression /anxiety	1	1	3
	Dysuria	3	0	0
	Vomiting	1	0	4
	Diarrhoea	3	0	9
	Blurred vision	2	0	3

Table 6.22 Number of adverse events attributable to ciclosporin and/or prednisolone (T1RA and T1RB: n=89)

4. Quality of life

This is the first time that the SF-36 questionnaire has been used in a leprosy clinical trial. Our Amharic translation was validated before using it in the ciclosporin trials.

All the comparisons were done on group mean quality of life scores and not on individual patient scores. There was no statistically significant difference in changes in all scores between patients on the ciclosporin arm and those on the prednisolone arm.

All the scores were significantly increased ($p<0.05$) between the start of the study and the end of the study except for the social functioning scale (SF) in patients with

acute T1R randomised to both treatment arms. For patients with chronic T1R, fewer SF-36 scales showed a statistically significant increase ($p>0.05$) during the study period, namely physical functioning, bodily pain, emotional role, mental health and the physical component summary scale. The data in the study with patients with chronic T1R may be skewed by the small sample size (n=11). We considered SF-36 results as statistically significant when at least one of the composite or scale scores showed a statistically significant difference, with p value <0.05, between the start and the end of the study. The effect is the difference between the scores at the start and those at the end of the study. Effect size was calculated and published guidelines were followed (Ware et al. 2005). Standardised mean differences of less than 0.30 standard deviations are considered small effects, 0.30-0.80 moderate, and more than 0.80 as large. Statistically significant differences, however, do not imply that a meaningful or relevant difference has been demonstrated for the individuals enrolled in such trials (Sloan et al. 2002).

To determine whether the observed changes in SF-36 scores were statistically and clinically meaningful, minimal clinically important changes (MCIC) for SF-36 subscales are needed. MCIC have not been studied in leprosy reactions so the closest we can come to defining these is by using the published standards for minimal "clinically and socially relevant" change in group scores as a measure of MCIC at a group level. The standards for clinically and socially relevant changes at a group level are based on Cohen's d, with minimal important change represented by a moderate effect size (0.50–0.79), which corresponds to at least 5-point change in scores on the 0–100 scale (5%)(Ware et al. 2005). Using these criteria, all the scores of the SF-36 scales improved by at least 5 point in the groups of patients with acute T1R randomized to both treatment arms, indicating that the improvement in quality of life was clinically and socially relevant, for both groups with no significant difference between the two groups. These criteria are not applicable to the summary component scores. It would be interesting to look at individual patients' MCIC, but further studies are need to investigate this in leprosy reactions.

Patients in both T1R studies had lower quality of life score than the Ethiopian population norms and lower than the general leprosy patients whose data was collected for the validation exercise (Chapter 4). Quality of life scores on recruitment were lower across all scales for the patients with chronic T1R compared to those

with acute T1R, in particular in the mental health score. This may reflect the burden of chronic illness on psychological health.

5. ENL

Six patients recruited with T1R went on to experience ENL during the study. Details of these patients are shown in Table 6.23.

Patient number	Study arm	Week in study at ENL occurrence	R-J classification	BI at recruitment
T1RA004	Cn	6	BL	2,3,2
T1RA041	P	6	BB	1,1,1
T1RB010	Cn	6	BB	2,3,3
T1RA029	Cn	10	BL	2,3,4
T1RA036	P	16	BL	6,5,5
T1RA015	P	28	BL	5,5,6
T1RA053	P	28	BL	4,3,3

Table 6.23 Patients in the T1R studies who experienced ENL

All these patient had a positive BI ranging between 1 and 6, and were categorised clinically as BB or BL. Patients experiencing both T1R and ENL can occur at this part of the spectrum which is known to be immunologically unstable. A clinical classification of either BB or BL was given to 11 patients who received ciclosporin for either acute or chronic T1R, and 14 patients who were in the prednisolone arm. The reaction treatment patients received did not affect their risk of developing ENL.

Although it is known that patients in the BB-BL-LL spectrum of leprosy may develop both T1R and ENL simultaneously and/or alternatively, there is a lack of published data on the frequency and risk factors for this phenomenon.

6. Reviewing the use of Clinical Severity Scale for T1R in the Ciclosporin trials

The Clinical Severity Scale was used to assess the severity of T1R in all the patients recruited to T1R trials, both acute and chronic. The severity was also assessed and graded by a second independent physician at each visit. A total of 89 patients were assessed and a total of 854 assessments were carried out, of these 25 had to be discarded as they were incomplete and thus had an invalid score. During the ciclosporin study nerve assessments of Sensory Testing and Voluntary Muscle Testing were done by the physiotherapist and results converted into the clinical severity scale by the physician.

The results of 829 T1R severity assessments were analysed.

The severity of the T1R in the patients recruited to the ciclosporin studies was categorised by the specialist as none in 243 (29%), mild in 260 (31%), moderate in 171 (21%) and severe in 155 (19%). Median scores and standard deviations for each category were none=1.00 ± 9.67; mild= 6.50 ± 9.68; moderate= 11.5 ± 10.53 and severe= 19.50 ± 12.81. The box-plot in Fig 6.2 illustrates the score distribution.

The differences between the group with no active reaction and the mild group, the mild group and the moderate group and finally the moderate group and the severe group all reached statistical significance ($p<0.001$). Nine outliers were noted, mostly in the "none" and "mild" category indicating individuals with a high severity score but clinically found to not be in active T1R or in mild T1R.

The clinical severity scale for T1R was used to analyse the change in severity of reaction with treatment.

In the development and validation study of the T1R severity scale, cut off points were determined with a consideration for the clinical meaning of a given score (Walker *et al.*, 2008). A mild T1R was characterized by a score of 4 or less; a moderate reaction with a score between 4.5 and 8.5 and a severe reaction with a score of 9 or more. The median scores in our 829 assessments were higher for each severity category (none=1.00; mild=6.50; moderate=11.5 and severe=19.50) suggesting that the scores could be increased for other reasons than active T1R.

Looking at the data collected, old nerve function impairment is the most obvious reason for an increased baseline score that does not respond to treatment and is not

taken into account by the physician grading the severity of the reaction. Thus a high score, resulting from old (greater than six months) loss of sensation may not equate to an active severe T1R, explaining the many outliners in the "None" and "Mild" categories in the Fig 6.2 box plot.

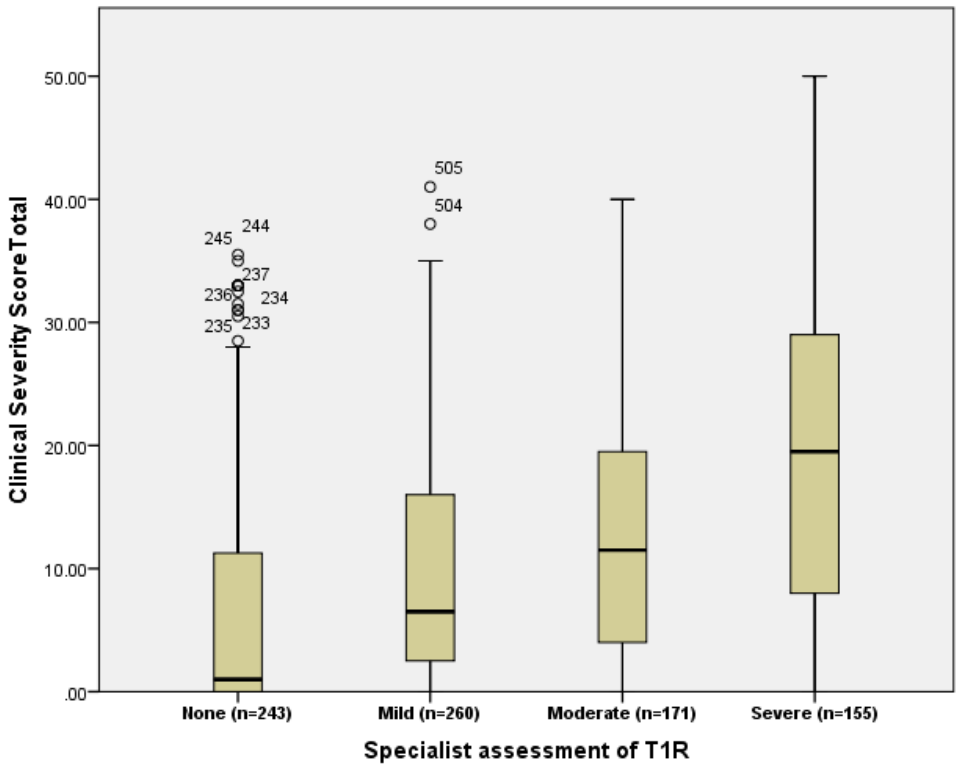


Figure 6.26 Box plot of T1R Severity Scores by specialist severity classification for patients in ciclosporin studies.

Equally a score of 0 may not equate clinically to a "no active T1R" finding. The developers of the T1R severity scale suggest that nerve damage of greater than six months duration should not be included in the severity score. This can be problematic as patients presenting for the first time may be unsure about the timing of the NFI and may have some acute NFI occurring on a background of old nerve damage.

Another issue noted with the severity scoring system is that of score distribution, in that the scale is severely weighted towards sensory and motor impairment. A patient with unaffected nerves but a severe skin T1R, may score up to 8 and be categorised as moderate, whereas most physician will consider this severe (especially in the presence of a facial patch) and treat accordingly. Nerve tenderness is another feature

often guiding physicians in the severity of a T1R, but this is not taken into account in this scoring system.

Trigeminal sensation which is part of the B score was not assessed in our study. It involves testing corneal sensation with a cotton bud, and this is rarely assessed in clinic because of hygiene reasons. To what extent this has affected the scores given is not known. Missing limbs also lead to a lower reaction severity score.

CHAPTER 7 RESULTS OF ENL STUDIES

Results of ciclosporin study in new ENL (Study ENLA)

Participants

Primary Outcome

Secondary outcomes

Summary of findings

Results of ciclosporin study in chronic or recurrent ENL (Study ENLB)

Participants

Primary Outcome

Secondary outcomes

Summary of findings

Discussion of ciclosporin in ENL pilot studies

The results of two pilot studies assessing the efficacy and safety of ciclosporin in comparison to prednisolone in the management of acute ENL and chronic ENL are presented in this chapter. Both studies were double blind randomized controlled studies in which patients received a 16 week course of either ciclosporin, with an initial four week course of prednisolone to cover the slow onset of action of ciclosporin, or prednisolone only. Following the 16 weeks of treatment (intervention period), patients were monitored for four months (follow-up period).

Erythema nodosum leprosum (ENL) was diagnosed when a patient had crops of tender subcutaneous skin lesions. There may have been accompanying fever (temperature >38°C), neuritis, joint pain, bone tenderness, orchitis, iritis oedema, malaise, anorexia and lymphadenopathy. New ENL was defined as the occurrence of ENL for the first time in a patient with lepromatous or borderline lepromatous leprosy. Recurrent or chronic ENL was defined by the presence of specific ENL symptoms in a patient who has had ENL previously treated with prednisolone and has had a flare-up or is still on prednisolone treatment but has poorly controlled ENL.

7.1 RESULTS OF CICLOSPORIN STUDY IN NEW ENL (STUDY ENLA)

7.1.1 Participants

Thirteen patients with newly diagnosed ENL were enrolled into trial ENLA between 12th August 2011 and 10th May 2012. Seven individuals were randomised into the ciclosporin arm (Figure 7.1).

The groups were not significantly different with respect to sex, age, Ridley-Jopling classification, or treatment with MDT (Table 7.1). Of this patient group with either BL or LL leprosy, 61% were newly diagnosed yet to start MDT. Only 3 patients presented with first ENL episode after finishing 12 months of MDT.

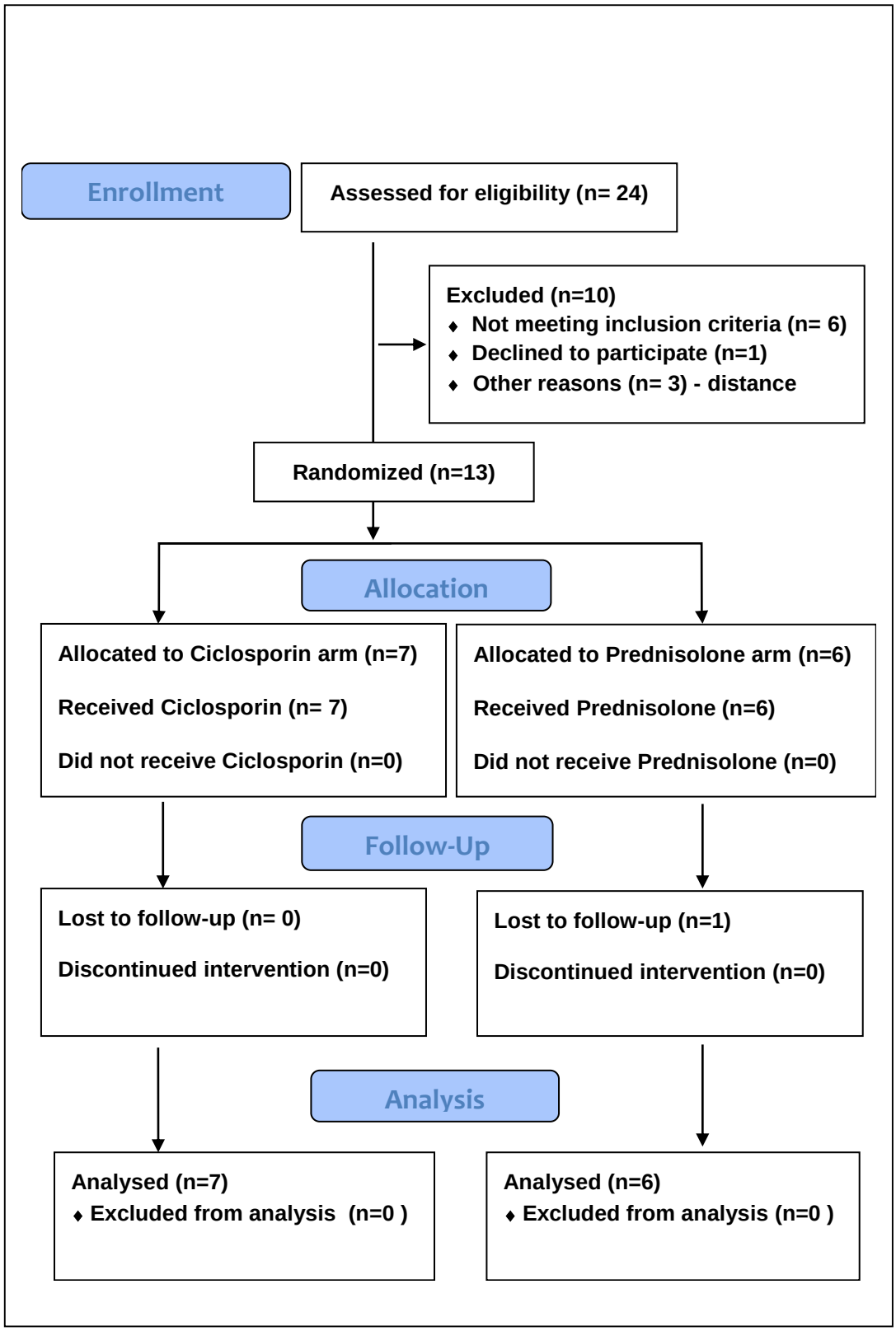


Figure 7.1 CONSORT diagram for ENLA study

Participants with new ENL		Ciclosporin (n=7)	Prednisolone (n=6)
Sex	Women: men	2:5	1:5
Median age (years)		30	30
Median eight (kg)		53.4 (41-76)	49.3 (38-76)
Ridley- Jopling	BL	2	2
	LL	5	4
Mean of mean BI	At diagnosis	4.4	3.4
	At recruitment	3.9	2
MDT status	Started at enrolment	5	3
	Current	1	1
	Completed	1	2
Co-morbidities and laboratory findings	Hypertension	1	None
	Dermatological	3	2
	Raised ESR	4	5
	Strongyloides in stool	2	0
EHF score (mean)		4.3	0.8

Table 7.1 Description of study participants in each arm of ENLA study

This study is too small to show any statistically significant difference between patients, but it can be noted that patients in the ciclosporin had a higher average BI at recruitment (3.9 versus 2) and more disability as reflected by the higher EHF score (4.3 versus 0.8).

Fungal conditions, such as tinea corporis or pityriasis versicolor were present in a third of patients and ESR was raised in 9 out of 13 patients.

ENL related findings are described in Table 7.2. ENL was graded as severe in 11 patients with five patients having ulcerated ENL nodules. Bone pain (92%) was the most common clinical feature associated with ENL, followed by peripheral oedema (85%) and neuritis (61%). Testicular tenderness was found in four of the male patients. Both study groups had similar baseline ENL findings.

Median duration in days patients were unwell with ENL prior to recruitment was much higher for the ciclosporin group (20 vs. 6).

Participants with new ENL			Ciclosporin (n=7)	Prednisolone (n=6)
Mean duration of ENL symptoms (days)			26.6 (5-63) median 20	10.5 (3-30) median 6
Severity of ENL	Severe		5	6
	Moderate		2	0
ENL symptoms	Nodules		7	6
	Sensory loss		6	5
	Weakness		4	6
	Tingling		5	6
	Joint pain		5	6
	Bone pain		4	5
	Testicular pain		2 /5	2 /5
	Pain in eyes		1	0
	Visual disturbance		1	1
ENL signs	No of new ENL nodules	1-5	0	1
		6-20	2	2
		>20	5	3
	Inflammation of ENL nodules*	EP	4	4
		EPF	0	0
		EPFU	3	2
	Nerve tenderness		4	4
	Tibial tenderness		7	5
	Oedema		5	6
	Joint swelling		2	1
	Lymphadenopathy		3	1
	Orchitis		2	0
	Fever		2	3
	Proteinuria		1	0
	Ocular signs		1	0

**EP= erythema and pain; EPF= erythema and pain plus function affected; EPFU= erythema and pain, function affected plus ulcerated nodules*

Table 7.2 ENL related findings at recruitment in ENLA

Incomplete follow up

One patient randomized to receive prednisolone was last reviewed at week 4. He withdrew from the study because a distant military posting made it impossible to attend for regular follow-up. His treatment was continued by the army doctor.

7.1.2 Primary outcome: Number of ENL recurrence episodes

Ten patients experienced one or more episodes of ENL recurrence. The mean number of ENL recurrence for the two treatment arm was 1.29 recurrences per patient in the ciclosporin arm and 2.4 recurrences per patient for the prednisolone arm (Table 7.3).

	CICLOSPORIN 7 patients	PREDNISOLONE 6 patients
Number of ENL flare-up episodes per patient	0	0*
	0	1
	1	4
	1	3
	3	2
	1	2
	3	
Mean	1.29	2.4

**This patient dropped out at week 4*

Table 7.3 ENL flare-up per patient (ENLA)

No significant difference between patients in the two treatment arms was detected with regards to number of ENL recurrences per patient (p= 0.149).

Timing of ENL flare-up in relation to treatment period is shown in Figure 7.2. The difference in the total numbers of ENL flare-up is due to fewer flare-ups occurring in ciclosporin group during the intervention period.

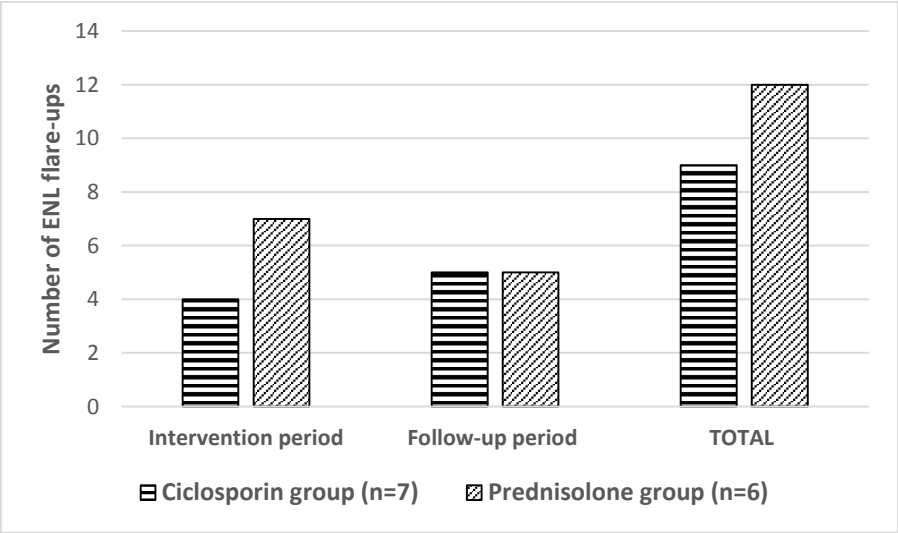


Figure 7.2 Number of ENL flare–up episodes per treatment period (ENLA)

7.1.3 Secondary outcomes

1. Time to ENL recurrence

Ten out of the 13 patients had an ENL recurrence, either during the treatment period (week 0 to 16) or the post treatment period (week 17-32). Time (in weeks) to the first recurrence episode of ENL after initiation of treatment is shown in (Figure 7.3).

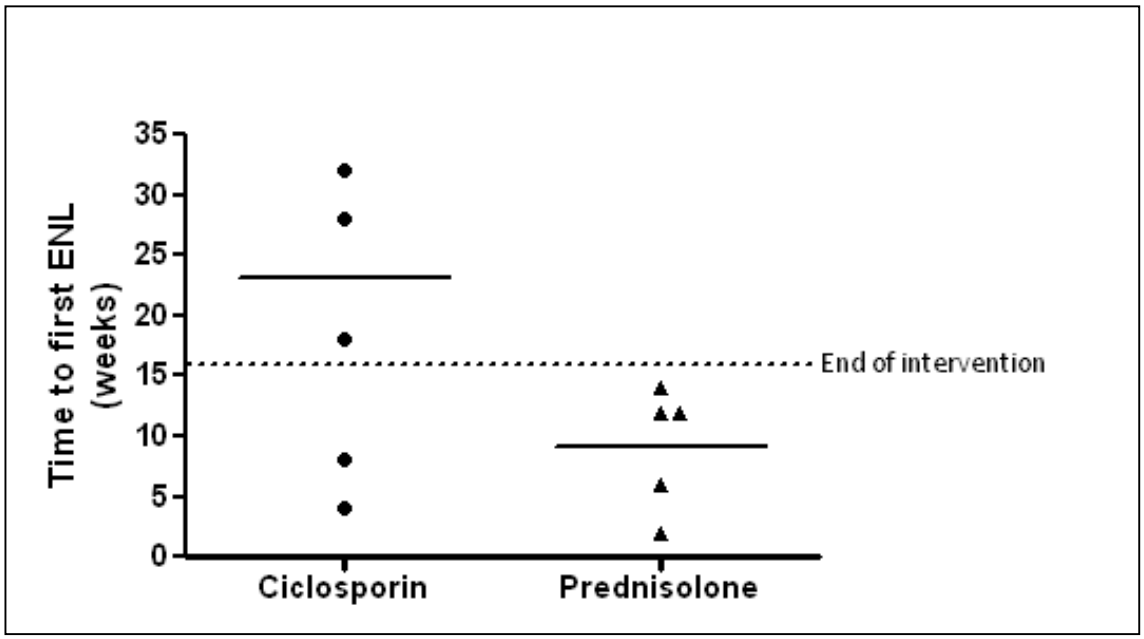
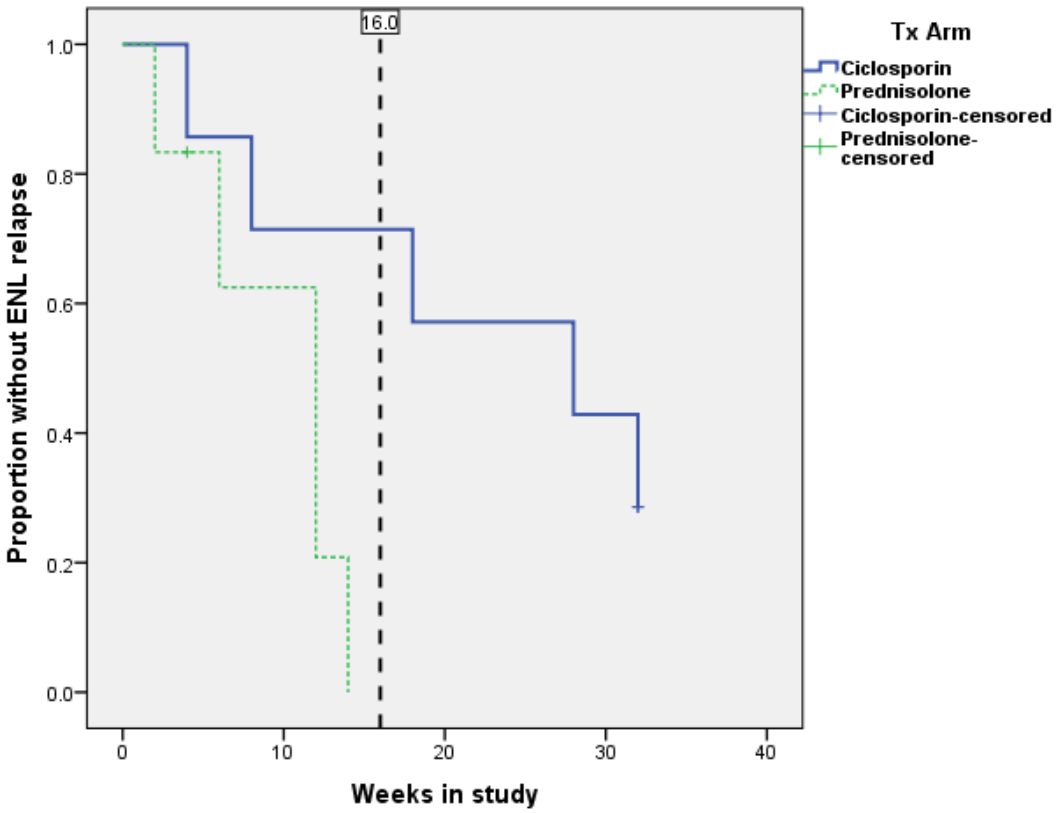


Figure 7.3 Time of first recurrence of ENL after initial control (group mean marked)

The mean time to first episode of ENL recurrence was 23 (median 28) weeks in the ciclosporin group and 9.2 (median 12) weeks in the prednisolone group. The patients in the prednisolone group thus appear to be experiencing the first ENL flare-up much earlier than those in the ciclosporin group. A Mann-Whitney U Test revealed no statistically significant difference (p=0.106) between time to first ENL recurrence for the ciclosporin group and the prednisolone group, probably because of the small sample size in this study.

The cumulative probability of ENL recurrence at a given point of time is shown on a Kaplan-Meier survival curve (Figure 7.4), and the significant difference between the two groups is a statistically significant. (Log Rank – Mantel Cox, p= 0.043).



**week 16 line represents the end of study intervention period*
(Overall Median= 17 weeks, 95%CI: 10.2-23.2)

Figure 7.4 Time to first ENL recurrence in ENLA study

2. Severity of ENL

Severity of ENL was rated in two ways: one was the physician's opinion on the severity, with the options of grading the ENL episode as none, mild, moderate or severe. The second grading took into account two components: a score for patient complaints of ENL symptoms and a score for physical findings related to ENL. This was part of the work for the severity scale for ENL. The ENL severity at recruitment and at recurrence for each patient in the study in shown in Table 7.4.

Study arm	Patient id	ENL severity at recruitment		Week # at flare-up	ENL Severity at recurrence	
		Score	Specialist opinion		Score	Specialist opinion
Ciclosporin (n=7)	001MGW	8;4	Severe	32	4;2	Moderate
	005WEC	6;4	Severe	No flare-up		
	007SMM	4;6	Moderate	No flare-up		
	009ADL	6;1	Moderate	28	4;5	Moderate
	011TEM	10;6	Severe	4	2;1	Mild
				8	6;4	Severe
				16	3;1	Moderate
	013KMS	11;7	Severe	8	6;4	Severe
	014ATS	14;7	Severe	18	5;4	Moderate
				24	5;4	Moderate
				32	3;4	Moderate
Prednisolone (n=6)	002MLA	9;8	Severe	6	3;1	Mild
	003GAB	7;6	Severe	12	2;1	Mild
				14	4;1	Moderate
				28	6;4	Moderate
	006HKD	6;6	Severe	2	9;3	Severe
				12	0;1*	Severe(on 35mg)
				20	2;1	Mild
	008SWG	7;7	Severe	Withdrew at week 4		
	010SSA	6;5	Severe	14	2;1	Mild
				24	4;3	Severe
				32	2;1	Mild
	012KKG	8;5	Severe	12	5;1	Moderate
				24	3;1	Mild

*Not assessed acutely prior to increase in steroids

Table 7.4 Severity of ENL at recruitment and at flare-up
for each participant, by severity score and by physician opinion (ENLA)

Patients on the ciclosporin arm had fewer ENL flare-up episodes during the treatment period (week 0-16) (Figure 7.5). The difference in severity grading of these episodes was not significantly different between the two treatment arms (p=0.687).

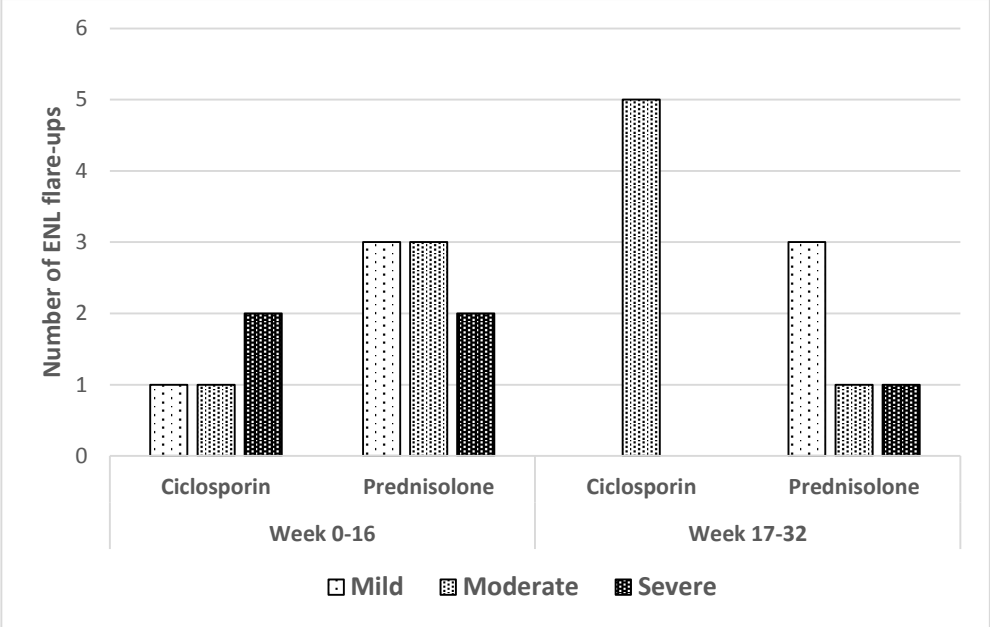


Figure 7.5 Number ENL flare-up episodes
(by ENL severity category in each study arm and treatment period (ENLA))

3. Amount of extra prednisolone

Ten out of the 13 patients received additional prednisolone. This was prescribed for ENL recurrence or for neuritis. Two patients in the ciclosporin group did not require any additional prednisolone, and no data are available on the one patient in the prednisolone only group who withdrew at week 4. Table 7.5 and Figure 7.6 show the mean amount of extra prednisolone required by patients in each treatment arms subdivided by treatment period.

Treatment Arm		Ciclosporin (n=7)	Prednisolone (n=5)	p- value (Mann-Whitney U test)
Mean extra prednisolone in mg	Tx period: wk 0-16	850	670	0.75
	F-up period: wk 17-32	1285	2035	0.22
	Total study period	2135	2705	0.74
Average total prednisolone in mg		2905	5785	0.028

Table 7.5 Mean amount of extra prednisolone required

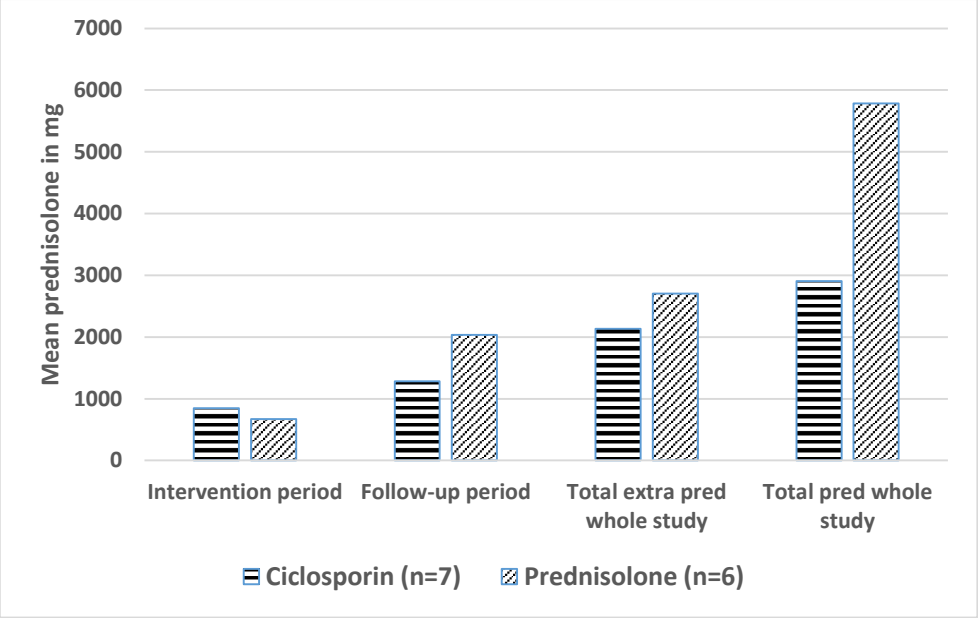


Figure 7.6 Mean amount of extra and total prednisolone prescribed

The mean amount of extra prednisolone needed during the 32 week long study was 21% less for the ciclosporin arm, suggesting that ciclosporin has a steroid sparing effect in the management of ENL.

The only significant difference in the amounts of prednisolone taken by participants in the two groups was in the overall total amount taken (p= 0.028). It is not possible to draw any conclusions from this, since the patients in the prednisolone arm are all on 3080mg of prednisolone as part of the treatment protocol. To further investigate the difference in amounts of additional prednisolone, the reasons for which the extra prednisolone was prescribed were subdivided as shown in Table 7.6 and Figure 7.7.

	Ciclosporin arm (n=7)		**Prednisolone (n=5)**	
Reason for additional prednisolone	**ENL**	**NFI/neuritis**	**ENL**	**NFI/neuritis**
Treatment period	**690mg (3)**	**160mg (1)**	**573mg (6)**	**98mg (1)**
Follow-up period	**572mg (6)**	**711mg (5)**	**1404mg (6)**	**630mg (1)**
TOT	**1262mg (9)**	**871mg (6)**	**1977mg (12)**	**728mg (2)**

Table 7.6 Mean amount of extra prednisolone required
by reason for prescription, in brackets number of episodes (ENLA)

During the 32 weeks of the study, patients in the prednisolone arm needed 36 % more additional prednisolone to control ENL recurrence (Figure 7.7). The difference rose to 60% in the follow up period (week 17-32). Both groups had the same number of ENL flare-ups in this period (6 each), so this difference in amount of extra prednisolone may reflect a difference in severity of ENL episodes. In contrast to this, patients on the ciclosporin arm needed more additional prednisolone throughout the study to control neuritis and NFI.

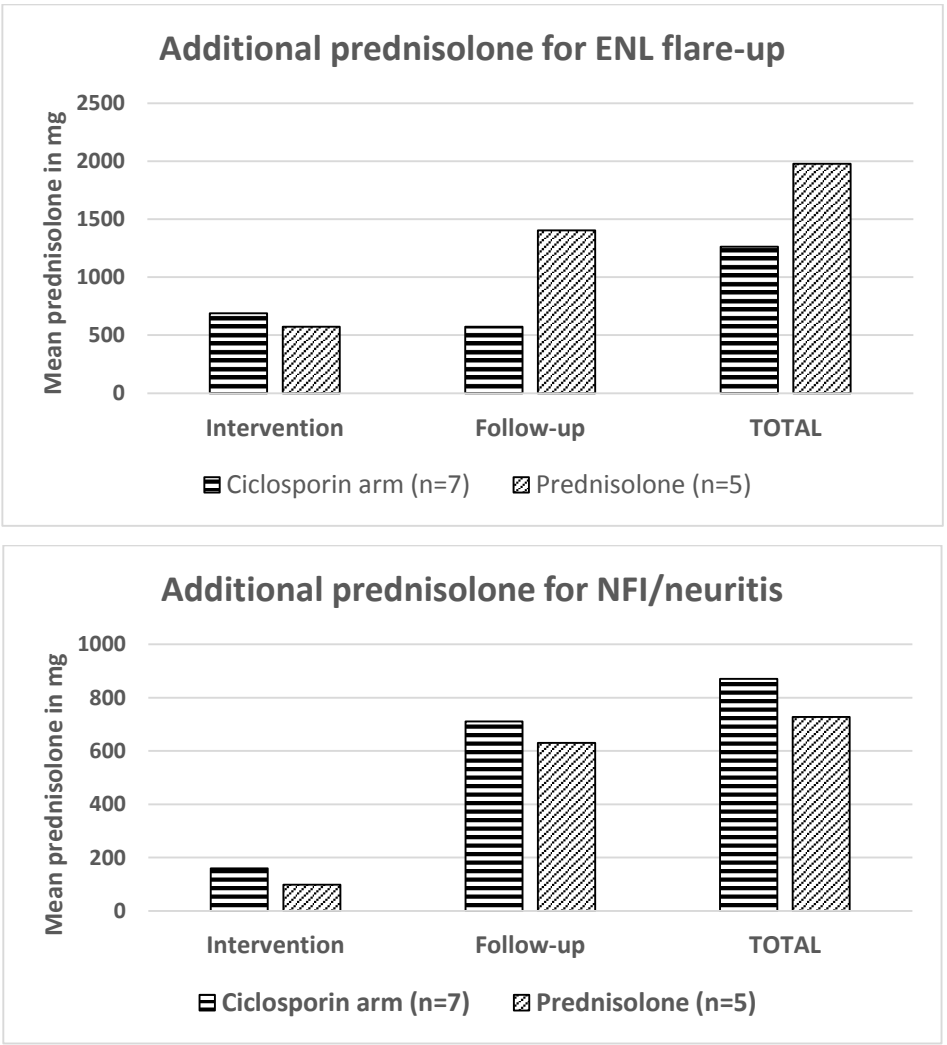


Figure 7.7 Mean amount of additional prednisolone needed by participants *to control ENL and NFI, categorised by treatment period (ENLA)*

Patients in the ciclosporin arm needed slightly more prednisolone for NFI and neuritis than those in the prednisolone arm. Looking at the nerve data in detail, 25% of nerves in patients treated with ciclosporin had new NFI, whereas the prednisolone group had 18% of nerves with new NFI. Although nerve function recovery rates

were similar for the two study arms, the ciclosporin groups had a higher chance of NFI recurrence, and a higher requirement for prednisolone.

4. Adverse Events

All 12 patients with new ENL who completed the study, experienced at least one adverse event. No patients had renal impairment during the study period. Those adverse events attributed to either prednisolone or ciclosporin are shown in Table 7.7 Patients in the ciclosporin arm who were receiving a large amount of additional prednisolone to control the reaction were also noted. The study is too small to detect any statistically significant difference.

	MINOR ADVERSE EVENTS	
	Ciclosporin arm (n=7)	**Prednisolone (n=6)**
Moon Face	**1***	**2**
Acne	**1**	**4**
Fungal infections	**2**	**3**
Gastric pain	**1***	**2**
	MAJOR ADVERSE EVENTS	
Infections	**5 (3*)**	**5**
Infected ulcers	**2 (1*)**	**3**
Hypertension	**1**	**0**
Hyperglycaemia	**0**	**2**

* PATIENTS ON HIGH DOSE EXTRA PREDNISOLONE

Table 7.7 Number of patients experiencing minor and major adverse events *related to ciclosporin and/ or prednisolone (ENLA)*

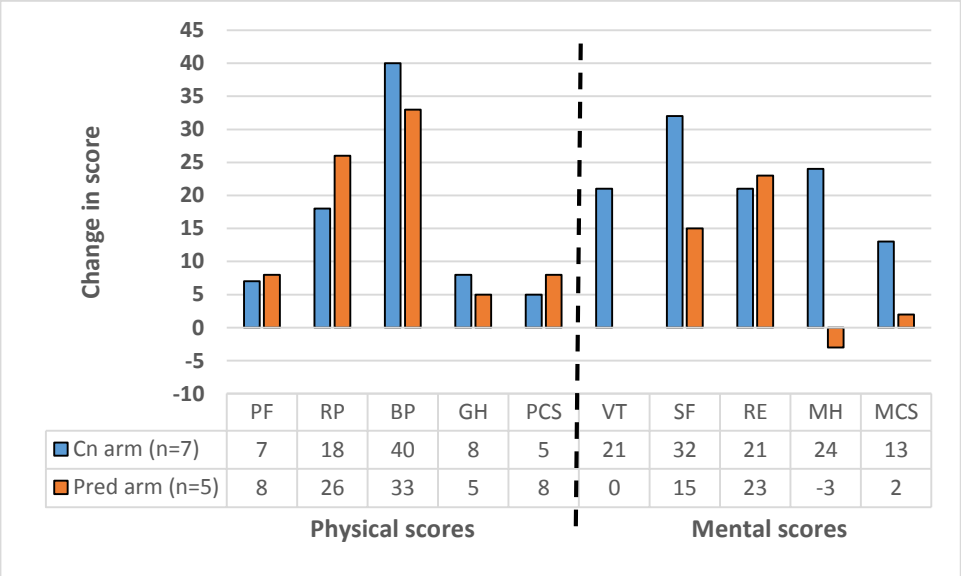
One patient experienced a serious adverse event which resulted in the amputation of the left big toe at week 16. This patient, on the ciclosporin arm of the study, had poorly controlled ENL requiring a total of 5355mg of additional prednisolone during the 32 weeks on the study, to control the ENL flare-ups. She developed an ulcer on the left big toe following a traumatic injury which despite antibiotic treatment progressed into osteomyelitis.

5. Quality of life

Patients completed our validated SF-36 health related quality of life questionnaire in Amharic at recruitment and at the end of the study. Of the 13 patients recruited with acute ENL, 12 had completed the end of study questionnaire, all of whom improved in all one or both physical and mental summary components.

Table 7.8 shows the mean group score for each SF-36 scale at the start and at the end of the study. For the seven patients in the ciclosporin group, there is statistically significant increase ($p>0.05$) in the scales of BP, VT, MH and the physical and mental component summary scale. For the five patients in the prednisolone group, the only significant increase in score is in the BP scale.

The difference in change in score, for each SF-36 scale, in patients with acute ENL recruited to different study arms is shown graphically in Figure 7.8.



	PF	RP	BP	GH	PCS	VT	SF	RE	MH	MCS
Cn arm (n=7)	7	18	40	8	5	21	32	21	24	13
Pred arm (n=5)	8	26	33	5	8	0	15	23	-3	2

Figure 7.8 Change in SF-36 scores between start and end of study ENLA

Bodily pain scale scores improved the most between the start and the end of the study, followed by physical role (RP) scores. The only significant difference was in the mental health score ($p=0.023$), although the small sample size makes the finding difficult to interpret.

Patients on Ciclosporin Arm

SF-36 variables ENLA	Baseline Mean ± SD	End of study Mean ± SD	Effect (Difference= end of study - baseline)			*p value* (paired sample t test)
			Mean ± SD	ES	ES description	
PF	79.3 ± 27.1	86.4 ± 16.3	7.1 ± 27.2	0.26	small	.513
RP	62.5 ± 25	80.4 ± 22.7	17.9 ± 34.9	0.71	moderate	.224
BP	23.9 ± 12.8	64.0 ± 28.1	40.1 ± 27.6	3.14	large	.009
GH	42.9 ± 14.1	50.7 ± 24.7	7.9± 32.8	0.56	moderate	.550
VT	42.0 ± 18.3	62.5 ± 17.7	20.5 ± 19.7	1.12	large	.033
SF	62.5 ± 38.2	94.6 ± 14.2	32.1 ± 40.7	0.84	large	.082
RE	58.3 ± 28.5	79.8 ± 22.5	21.4 ± 35.6	0.75	moderate	.163
MH	45.0 ± 8.2	68.6 ± 18.0	23.6 ± 16.0	2.87	large	.008
PCS	44.3 ± 5.3	49.5 ± 6.7	5.2 ± 5.0	0.99	large	.032
MCS	37.0 ± 9.1	49.6 ± 6.1	12.6 ± 10.6	1.38	large	.020

Patients on Prednisolone Arm

SF-36 variables ENLA	Baseline Mean ± SD	End of study Mean ± SD	Effect (Difference= end of study - baseline)			*p value* (paired sample t test)
			Mean ± SD	ES	ES description	
PF	54.3 ± 35.7	82.0 ± 20.1	27.8 ± 43.0	0.65	moderate	.002
RP	34.3 ± 31.6	64.8 ± 20.5	30.6 ± 38.7	0.79	moderate	.000
BP	28.9 ± 23.4	70.4 ± 25.6	41.5 ± 34.0	1.22	large	.000
GH	39.8 ± 18.6	50.3 ± 20.0	10.6 ± 21.2	0.5	moderate	.015
VT	48.8 ± 19.9	60.6 ± 19.1	11.8 ± 25.3	0.47	moderate	.023
SF	74.1 ± 33.2	85.6 ± 26.6	11.6 ± 41.6	0.28	small	.160
RE	33.3 ± 29.9	74.7 ± 22.2	41.4 ± 39.9	1.04	large	.000
MH	45.9 ± 21.7	63.3 ± 14.9	17.4 ± 22.8	0.76	moderate	.001
PCS	38.9 ± 9.8	48.6 ± 7.0	9.7 ± 12.5	0.78	moderate	.000
MCS	38.0 ± 10.4	47.0 ± 6.7	9.0 ± 10.2	0.88	large	.000

PF-physical functioning, RP-role physical, BP-bodily pain, GH-general health perceptions, VT-vitality, SF-social functioning, RE-role emotional, MH-mental health, PCS-physical component summary, MCS-mental component summary
SD= standard deviation;
ES= effect size= mean (effect)/ SD (baseline)

Table 7.8 Mean group scores and the effect in difference in scores for ENLA study

7.1.4 Summary of findings of ciclosporin study in new ENL

The patients with new ENL randomized to the ciclosporin arm of the study showed a delay of 14 weeks (23 vs. 9.2 weeks) in the mean number of weeks to the first episode of ENL recurrence compared to the patients in the prednisolone arm.

Patients who received ciclosporin had fewer ENL recurrence episodes (9 vs 12), especially during the intervention period (week 0-16). Two patients in this group had no ENL recurrence.

During the follow-up period (week 17-32), the ciclosporin group had less severe ENL recurrence episodes, and required 60% less additional prednisolone.

The patients in the ciclosporin group needed more additional prednisolone to control isolated NFI and or neuritis.

A higher rate of minor adverse events was observed in the patients on the prednisolone arm and in patients taking large amounts of additional prednisolone.

The quality of life as measured by the eight SF-36 scales and the physical and mental summary components, generally improved for patients with new ENL in both study arms. More scales showed significant improvement in the ciclosporin arm patients. There was no significant difference between study arms, except in the mental health score, where the ciclosporin group had a better improvement. The small sample size makes interpretation of results difficult.

7.2 RESULTS OF CICLOSPORIN STUDY IN CHRONIC OR RECURRENT ENL (ENLB)

7.2.1 Participants

Twenty patients with chronic or recurrent ENL were enrolled into trial ENLB between 12th August 2011 and 20th February 2012 (Figure 7.9). Ten individuals were randomised into the ciclosporin arm.

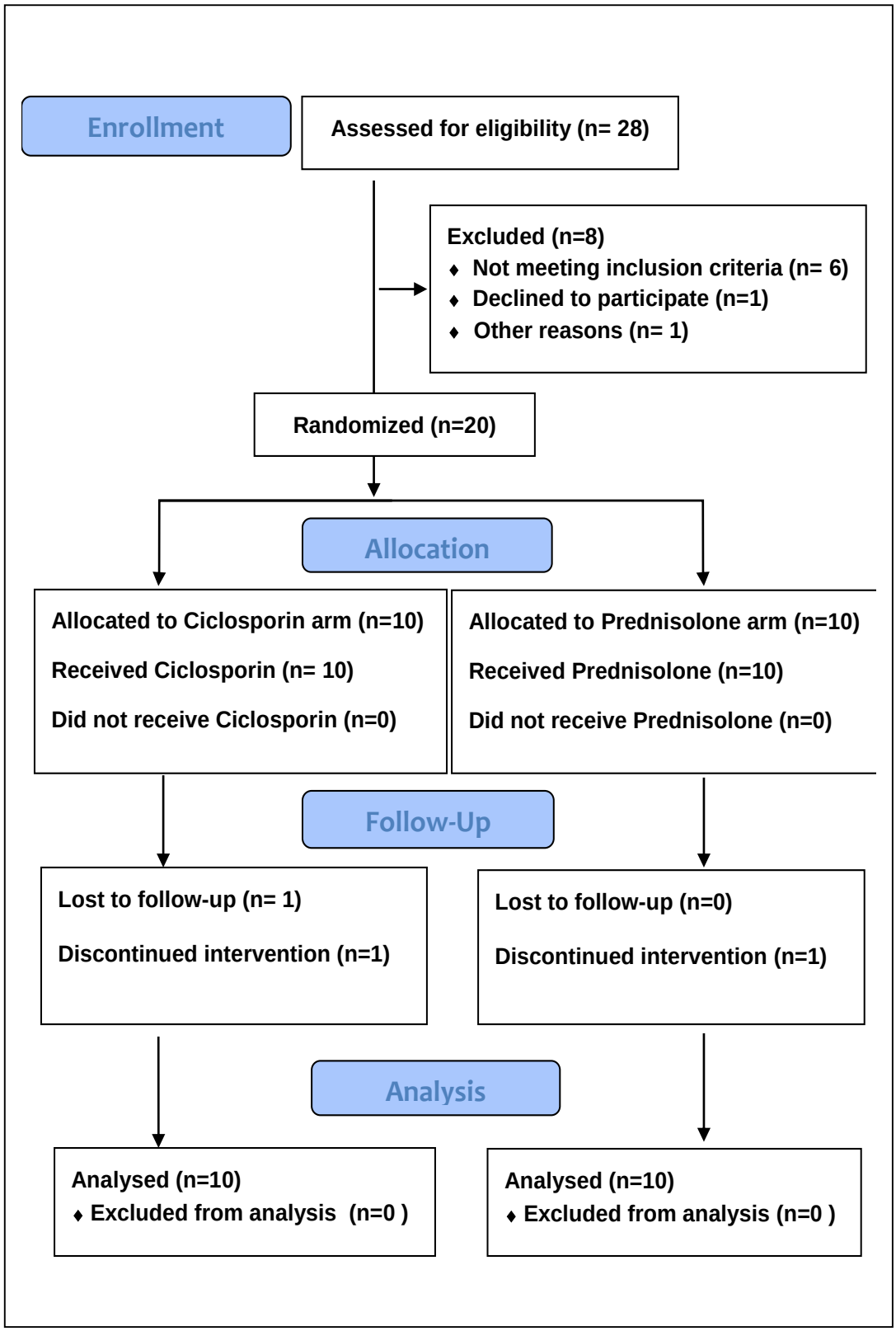


Figure 7.9 CONSORT diagram for ENLB

The participants in the two treatment arms were similar with respect to sex, age, Ridley-Jopling classification, or treatment with MDT (Table 7.9).

Participants with chronic ENL		Ciclosporin (n=10)	Prednisolone (n=10)
Sex	Women: men	2:8	2:8
Median age (years)		27	30
Median weight (kg)		56.0 (45-70)	54.9 (44 -70)
Ridley- Jopling	BL	4	6
	LL	6	4
Mean of mean BI	At diagnosis	3	3.25
	At recruitment	1.3	0.9
MDT status	Started at enrolment	1	0
	Currently	2	2
	Completed	7	8
Co-morbidities and laboratory findings	Cholecystitis	1	0
	Hypertension	1	0
	Diabetes	0	1
	Gastric pain	2	4
	Dermatological	3	3
	Moon face	4	3
	Raised ESR	6	4
	Strongyloides in stool	0	1
EHF score (mean)		3.5	0.6

Table 7.9 Description of study participants in each arm for study ENLB

Most of the patients (15 out of 20) had completed 12 months of MDT. One patient started MDT at enrolment. He presented with a high BI, as a relapse from monotherapy treatment received 20 years earlier. Four patients on MDT at recruitment were patients who were diagnosed with relapse of leprosy after full course of MDT. This was confirmed by the appearance of new signs of leprosy or a higher BI than at first diagnosis. The patients in the ciclosporin group had higher disability EHF score (3.5 versus 0.6).

On average, patients with chronic or recurrent ENL had been on prednisolone for a period of two years prior to recruitment into the study (range was six months to five years). Many patients had one or more side effects attributable to prednisolone use prior to recruitment: moon face (35%), acne or fungal skin infections (30%), dyspepsia (30%) and one patient had elevated blood sugar. ESR was raised in 10 out of 20 patients.

ENL related findings are shown in Table 7.10. Most patients, 18 out of 20, had severe ENL. Nerve tenderness occurred in 85% of patients with chronic ENL, 70 % had bone tenderness, and 65% peripheral oedema. Pyrexia was only present in 7 out of the 20 patients (35%). Six men reported testicular pain. The frequency in positive ENL symptoms and signs are similar between the two study groups.

Participants with chronic ENL			**Ciclosporin (n=10)**	**Prednisolone (n=10)**
Mean duration of ENL symptoms (days)			**13.8 (1-30) median 15**	**7.6 (2-28) median 7**
Mean prednisolone dose at recruitment in mg (group)			**19.5**	**17.5**
Severity of ENL	**Moderate**		**2**	**0**
	Severe		**8**	**10**
ENL symptoms	**Nodules**		**10**	**9**
	Sensory loss		**7**	**5**
	Weakness		**7**	**4**
	Tingling		**8**	**7**
	Joint pain		**7**	**7**
	Bone pain		**7**	**6**
	Testicular pain		**1 /5**	**5 /5**
	Pain in eyes		**1**	**6**
	Visual disturbance		**0**	**4**
ENL signs	**No of new ENL nodules**	**1-5**	**1**	**1**
		6-20	**7**	**5**
		>20	**2**	**4**
	Inflammation of ENL nodules*	**EP**	**5**	**7**
		EPF	**3**	**2**
		EPFU	**2**	**1**
	Nerve tenderness		**9**	**8**
	Tibial tenderness		**5**	**8**
	Oedema		**6**	**7**
	Joint swelling		**1**	**6**
	Lymphadenopathy		**1**	**2**
	Orchitis		**1**	**4**
	Fever		**2**	**5**
	Proteinuria		**2**	**4**
	Ocular signs		**1**	**3**

**EP= erythema and pain; EPF= erythema and pain plus function affected; EPFU= erythema and pain, function affected plus ulcerated nodules*

Table 7.10 ENL related findings at recruitment in ENLB

The main difference of note is that the mean duration of days patients were unwell with ENL recurrence prior to recruitment is higher for the ciclosporin group (13.8 vs. 7.6).

Incomplete follow up

Three patients did not complete the full schedule of follow-up. One patient in the prednisolone arm, last reviewed at week 11, died. The second patient, on the ciclosporin arm, developed acute renal failure and was withdrawn from the study. The third patient did not attend the week 6 review and self–withdrew from the study. Both these patients continued on prednisolone treatment at their nearest health centres.

7.2.2 Primary outcome: Number of ENL flare-up episodes

Seventeen patients experienced one or more episodes of ENL recurrence. The mean number of ENL recurrence for the two treatment arm was 2.3 recurrences per patient in the ciclosporin arm and 2.0 recurrence per patient for the prednisolone arm (Table 7.11).

	CICLOSPORIN 10 patients	PREDNISOLONE 10 patients
Number of ENL flare-up episodes per patient	0	0
	1	0
	1	1
	2	1
	2	1
	2	2
	3	3
	3	4
	4	4
	5	4
Mean	2.3	2

Table 7.11 ENL flare-up per patient (ENLB)

Patients in the two treatment arms had no significant difference in the mean number of ENL recurrences per patient (Mann-Whitney U Test, p= 0.684). The difference in number of ENL recurrences between the two study arms, is largest during the treatment period with more episode occurring in the ciclosporin arm (Figure 7.10).

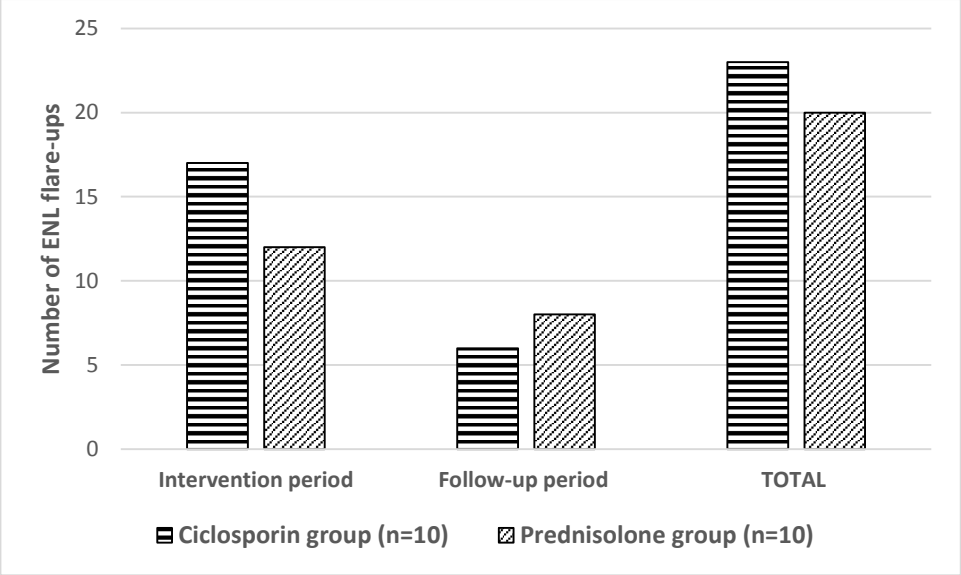


Figure 7.10 Number of ENL flare-up episodes per treatment period (ENLB)

7.2.3 Secondary outcomes

1. Time to ENL recurrence

Seventeen out of 20 patients had an ENL recurrence either during the treatment period (week 0-16) or the post treatment period (week 17-32).

The mean time to first episode of ENL recurrence was 7.1 weeks (median=4) in the ciclosporin group and 11.25 (median=12) weeks in the prednisolone group. There is no significant difference between time to first ENL recurrence for the two groups (Mann-Whitney U Test, p=0.114).

Figure 7.11 shows a cluster of ENL recurrence cases around week 4 amongst the patients in the ciclosporin arm. This is probably due to the prednisolone being decreased to 10mg and stopped at week 4. At recruitment, 8 out of 10 of these patients had active ENL despite being on a daily prednisolone on or above of 15 mg. The cumulative probability of ENL recurrence in the two groups at any given point of time is shown on a Kaplan-Meier survival curve (Figure 7.12), and they are not statistically different (Log Rank – Mantel Cox, p= 0.213).

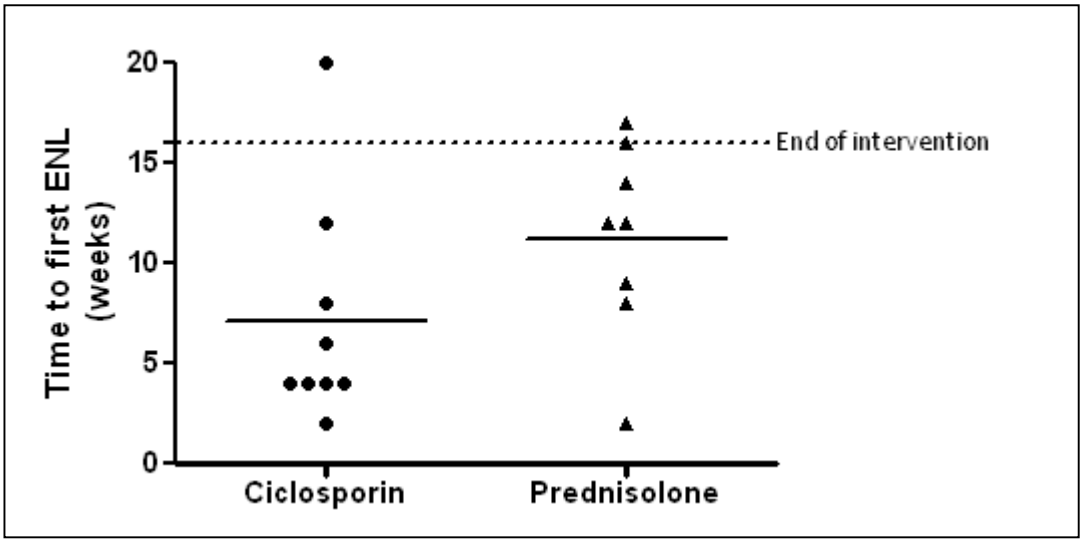
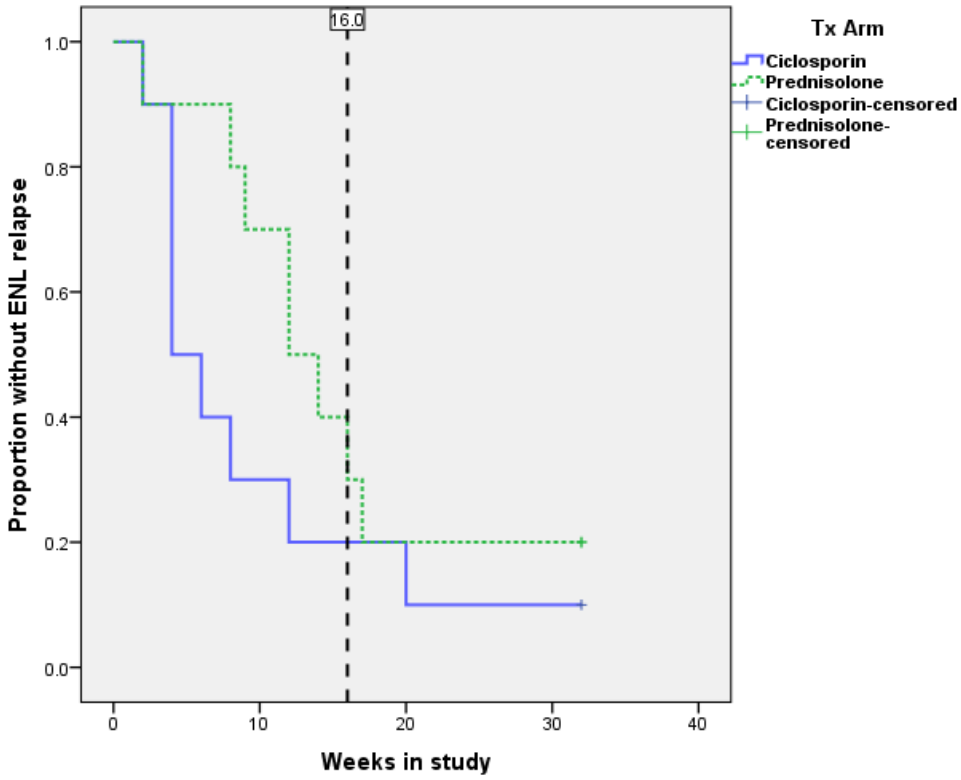


Figure 7.11 Time of first recurrence of ENL after initial control – ENLB



**week 16 line represents the end of study intervention period*
(Overall Median= 12.5 weeks, 95%CI: 8.3-16.7)

Figure 7.12 Time to first ENL recurrence - ENLA study

2. Severity of ENL

The ENL severity at recruitment and at recurrence for each patient was scored as in the ENLA study and is shown in Table 7.12.

Ciclosporin arm (n=10)					
Patient id	**ENL severity at recruitment**		**Week number at flare-up**	**ENL severity at flare-up**	
	Score	**Specialist opinion**		**Score**	**Specialist opinion**
004FMB	9;6	severe	**12**	2;2	mild
			16	6;3	severe
005MAG	6;3	severe	**4**	8;7	severe
			6	6;5	severe
			8	5;4	severe
			16	4;1	severe
			32	8;3	severe
006GEM	6;5	severe	**4**	5;3	severe
			5	12;8	severe
			8	3;0	moderate
009ZFA	5;3	moderate	**20**	3;0	moderate
			22	2;1	mild
			24	3;6	moderate
010TAS	8;6	severe	**6**	6;6	severe
			10	8;6	severe
011THT	6;5	moderate	**4**	7;5	severe
013BMB	11;4	severe	**4**	6;6	severe
			12	4,1	moderate
			16	5;1	severe
			20	2;1	moderate
014AEG	4;4	severe	**No flare-up**		
020GGG	7;6	severe	**8**	6;3	moderate
			10	9;7	severe
			18	11;3	severe
021HHU	4;6	severe	**2**	3;5	severe
			10	10;6	severe

Table continued…….

Prednisolone arm (n=10)					
Patient id	**ENL severity at recruitment**		**Week number at flare-up**	**ENL severity at flare-up**	
	Score	**Specialist opinion**		**Score**	**Specialist opinion**
001DFM	8;1	severe	**14**	6;5	severe
			16	4;2	mild
			24	3;4	moderate
			32	7;3	severe
002MTD	7;6	severe	**17**	6;5	severe
003AYE	2;3	severe	**16**	3;2	mild
007TBT	8;7	severe	**No flare-up**		
008RKG	7;8	severe	**No flare-up**		
012IAI	9;4	severe	**9**	9;7	severe
			28	3;1	mild
			32	7;4	severe
016TMW	9;5	severe	**12**	2;2	moderate
			24	2;2	mild
017MHT	8;8	severe	**2**	7;5	severe
			4	9;5	severe
			5	10;8	severe
			7	6;0	severe
018ECT	9;6	severe	**12**	2;4	mild
			16	4;3	moderate
			20	3;1	moderate
			24	4;2	moderate
019DWB	9;5	severe	**8**	3;5	moderate

Table 7.12 Severity of ENL at recruitment and at flare-up
for each participant, by severity score and by physician opinion, for each treatment arm of ENLB

Patients receiving ciclosporin had almost twice as many severe (physician opinion), flare-ups in the intervention period (week 0-16) than patients receiving prednisolone only (Figure 7.13). This was statistically significant (p=0.017).

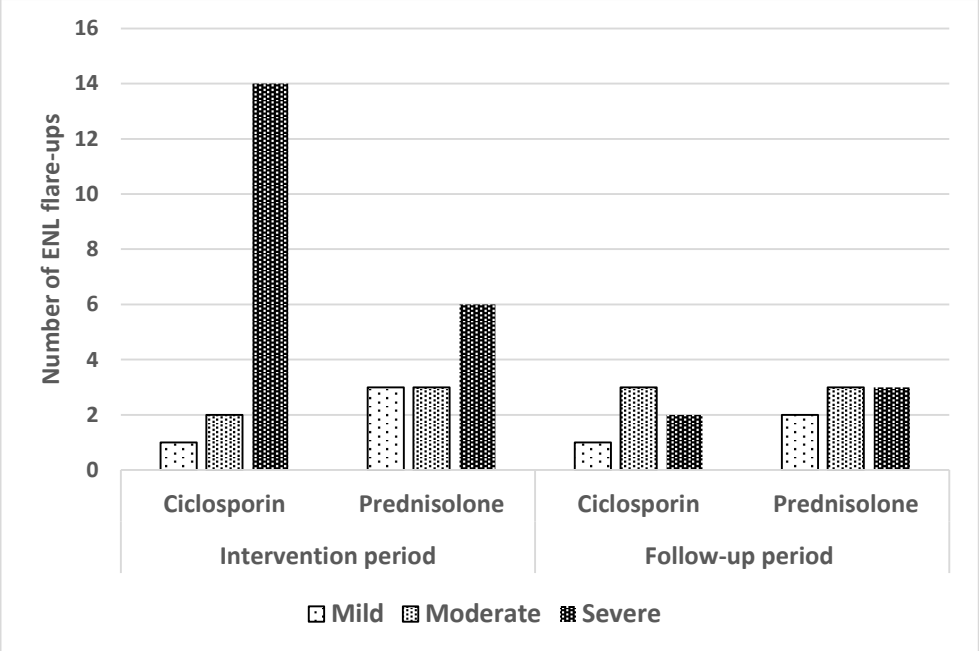


Figure 7.13 Number ENL flare-up episodes
by ENL severity category in each study arm and treatment period (ENLB)

3. Amount of extra prednisolone

The eight patients in the ciclosporin arm who completed the study and all ten patients in the prednisolone arm received additional prednisolone. Additional prednisolone was prescribed for ENL recurrence or for NFI/neuritis. The mean amount of extra prednisolone required by patients in each treatment arms, and for each treatment period is shown in Table 7.13 and Figure 7.14.

TREATMENT ARM		Ciclosporin (n=8)	Prednisolone (n=10)	p-value (M-W test)
Average extra Prednisolone in mg	Tx period: wk 0-16	1780	690	0.55
	F-up period: wk 17 -32	2290	1723	0.167
	Total study period	4070	2240	0.016
Average total pred in mg		4840	5319	0.460

Table 7.13 Mean amount of extra prednisolone prescribed (ENLB)

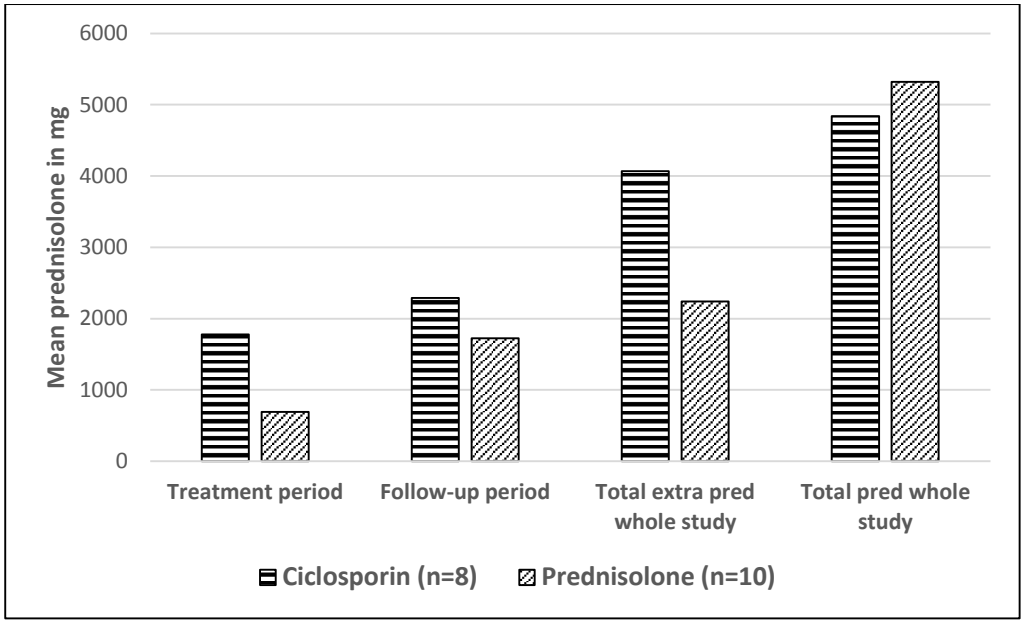


Figure 7.14 Mean amount of extra prednisolone prescribed *per treatment arm and study period (ENLB)*

The mean amount of extra prednisolone required during the 32 weeks of the study was almost double for the patients in the ciclosporin arm compared to those in the prednisolone arm (p= 0.016) (Figure 7.14).

In Table 7.14, the reason for extra prednisolone requirement is subdivided into ENL and neuritis/NFI, showing that, for most of the patients in this study, additional prednisolone was prescribed for ENL flare-up.

	Ciclosporin arm (n=8)		Prednisolone (n=10)	
	ENL	NFI/neuritis	ENL	NFI/neuritis
Wk 0-16	1708mg (17)	72mg (2)	690mg (12)	0
Wk 17-32	1763mg (6)	525mg (5)	1583mg (8)	140mg (3)
TOT	3471mg (23)	597mg (7)	2273mg (20)	140mg (3)

Table 7.14 Mean amount of extra prednisolone required *by reason for prescription, in brackets number of episodes.*

Patients in the ciclosporin arm needed 35 % more additional prednisolone to control ENL flare-up than those in the prednisolone arm. The difference was highest in the treatment period (week 0-16), as ENL flare-up episodes were greater in number as well as more severe. Patients in the ciclosporin arm needed more prednisolone for

NFI and neuritis than those in the prednisolone arm. Looking at the nerve data in detail, 42% of nerves in patients treated with ciclosporin had new NFI, whereas the prednisolone group had 30% of nerves with new NFI. Although nerve function recovery rates were similar for the two study arms, the ciclosporin groups had a higher chance of NFI recurrence.

4. Adverse Events

All 20 patients in the study reported at least one adverse event. As all patients had been on prednisolone for varying length of times at recruitment, some were already experiencing prednisolone side effects (Table 7.15). Patients who were receiving more than the average amount of extra prednisolone are also marked.

DRUG RELATED ADVERSE EVENT		Ciclosporin arm (n=10)	Prednisolone (n=10)
MINOR ADVERSE EVENTS	Moon Face	4 (3#, 1*)	4 (3#)
	Acne	5 (2#, 2*)	6 (2#)
	Fungal infections	3 (1#, 2*)	9 (1#)
	Gastric pain	8 (3#, 3*)	10 (3#)
MAJOR ADVERSE EVENTS	Infections	7 (1#, 4*)	10 (2#)
	Infected ulcers	4 (2*)	4
	Hypertension	1*	0
	Hyperglycaemia/diabetes	1*	2
	Nocturia	0	3 (1#)
OTHER ADVERSE EVENTS	Night sweats	0	2 (1#)
	Hypertrichosis	1	0
	Gum hyperplasia	1	0
	Anxiety	0	1
	Depression	1*	0

PATIENTS WITH PRE-EXISTING SIDE EFFECT, * PATIENTS ON HIGH DOSE EXTRA PREDNISOLONE

Table 7.15 Number of patients experiencing minor and major adverse events *related to ciclosporin and/ or prednisolone (ENLB)*

Table 7.16 details the five serious adverse events occurred in this study ENLB; four were attributable to prednisolone and one to ciclosporin.

Age/ Sex	Study arm	Week number of event	Adverse event	Grading	Receiving prednisolone	Pre-existing morbidity	Causality	Outcome
23/ M	Cn	5	Acute renal failure	3	NO	Vomiting (unknown cause) and dehydration	Possibly caused by ciclosporin	Ciclosporin stopped No sequelae
22/ F	Cn	9	Diabetic keto-acidosis	4	YES (60mg/d)	Severe ENL, poorly controlled and on prednisolone for 25 months, Slightly elevated blood glucose at recruitment	Definitely related to prednisolone	Insulin started, continued ciclosporin, very low dose prednisolone used. On oral hypoglycaemic six months later.
23/ M	Cn	20	Necrotising fasciitis	4	YES (60mg/d)	On prednisolone for 20 months. Finished ciclosporin 4 weeks previously. Needed extra prednisolone +++. Recent furunculosis. Spread of cellulitis to face and pinnae	Most probably related to prednisolone – immune-suppression	Deformed pinnae – awaiting plastic reconstruction
45/ F	P	4	Diabetes	3	YES	Elevated fasting blood sugar at recruitment On prednisolone for 24 months	Definitely related to prednisolone	Started on oral hypoglycaemic
24/ F	P	12	Miliary tuberculosis	4	NO	On prednisolone for 18 months	Definitely related to prednisolone – immune-suppression	TB treatment given for 8 months No sequelae
28/ M	P	11	Death	5	YES (80mg/d)	Severe ENL, poorly controlled and on prednisolone for 36 months. Dyspepsia , on PPI	Definitely related to prednisolone	Perforated peptic ulcer; peritonitis; multi-organ failure; death

Cn: ciclosporin arm; P: prednisolone arm

Grading: 1= Mild; 2= Moderate, 3= Severe; 4= Life-threatening or disabling; 5= Death (according National Cancer Institute Adverse Event Grading system –CTCAE)

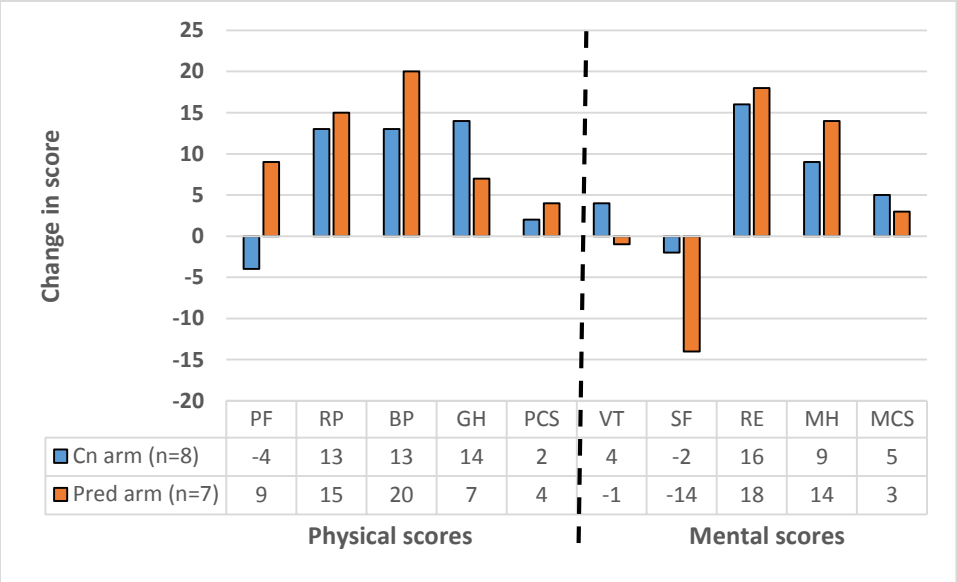
Table 7.16 Serious adverse events in study ENLB

5. Quality of life

Patients completed our validated SF-36 health related quality of life questionnaire in Amharic at recruitment and at the end of the study. Of the 20 patients recruited with chronic ENL, 15 had completed the end of study questionnaire, six of whom improved and one scored less in both physical and mental summary components. The other eight patients improved in only one of the two summary components.

Table 7.17 shows the mean group score for each SF-36 scale at the start and at the end of the study. There was no statistically significant difference in score changes for any of the SF-36 scales for both groups of patients on the two different treatment arms.

The changes in score, for each SF-36 scale, in patients with chronic ENL recruited to different study arms is shown graphically in Figure 7.15.



	PF	RP	BP	GH	PCS	VT	SF	RE	MH	MCS
Cn arm (n=8)	-4	13	13	14	2	4	-2	16	9	5
Pred arm (n=7)	9	15	20	7	4	-1	-14	18	14	3

Figure 7.15 Change in SF-36 scores between start and end of study ENLB

Bodily pain scale scores improved the most between the start and the end of the study, for the prednisolone group, followed by emotional role (RE) for both groups of patients. There was a large decrease in social function score for the patients on prednisolone only, although because of the small sample size, it was not found to be statistically significant.

Patients on Ciclosporin Arm

SF-36 variables ENLB	Baseline Mean ± SD	End of study Mean ± SD	Effect (Difference= end of study - baseline)			*p value* (paired sample t test)
			Mean ± SD	ES	ES description	
PF	73.7 ± 19.7	70.0 ± 32.1	-3.7 ± 41.3	0.19	small	.807
RP	45.3 ± 31.1	58.6 ± 28.5	13.3 ± 33.0	0.43	moderate	.292
BP	29.6 ± 31.7	42.8 ± 24.5	13.1 ± 35.5	0.41	moderate	.330
GH	37.6 ± 10.4	51.6 ± 23.0	14.0 ± 24.7	1.35	large	.143
VT	41.1 ± 11.0	45.3 ± 12.8	4.2 ± 15.0	0.38	moderate	.457
SF	60.7 ± 31.8	60.9 ± 34.4	-1.8 ± 51.8	0.06	small	.930
RE	44.8 ± 29.9	60.4 ± 28.8	15.6 ± 32.3	0.52	moderate	.213
MH	46.9 ± 19.1	55.6 ± 13.5	8.8 ± 15.1	0.46	moderate	.144
PCS	42.1 ± 5.4	44.4 ± 8.9	2.3 ± 6.9	0.42	moderate	.378
MCS	35.7 ± 6.4	40.5 ± 10.7	4.8 ± 7.1	0.75	moderate	.097

Patients on Prednisolone Arm

SF-36 variables ENLB	Baseline Mean ± SD	End of study Mean ± SD	Effect (Difference= end of study - baseline)			*p value* (paired sample t test)
			Mean ± SD	ES	ES description	
PF	73.6 ± 34.1	82.9 ± 15.5	9.3 ± 25.7	0.27	small	.377
RP	42.0 ± 20.3	57.1 ± 15.9	15.2 ± 21.9	0.75	moderate	.116
BP	30.1 ± 19.1	49.9 ± 9.1	19.7 ± 23.7	1.03	large	.070
GH	37.9 ± 13.5	44.7 ± 19.2	6.9 ± 27.4	0.51	moderate	.533
VT	52.7 ± 17.6	51.8 ± 10.7	-0.9 ± 8.4	0.05	small	.788
SF	89.3 ± 28.3	75.0 ± 22.8	-14.3 ± 31.8	0.50	moderate	.280
RE	39.3 ± 28.3	57.1 ± 23.3	17.9 ± 39.8	0.63	moderate	.280
MH	42.1 ± 7.0	55.7 ± 14.0	13.6 ± 17.0	1.94	large	.079
PCS	42.9 ± 8.3	46.7 ± 3.4	6.9 ± 3.8	0.46	moderate	.165
MCS	38.1 ± 5.9	40.9 ± 8.0	2.7 ± 9.0	0.46	moderate	.451

PF-physical functioning, RP-role physical, BP-bodily pain, GH-general health perceptions, VT-vitality, SF-social functioning, RE-role emotional, MH-mental health, PCS-physical component summary, MCS-mental component summary
SD= standard deviation;
ES= effect size= mean (effect)/ SD (baseline)

Table 7.17 Mean group scores and the effect in difference in scores for ENLB study

7.2.4 Summary of ciclosporin study in chronic or recurrent ENL

The patients with chronic or recurrent ENL randomized to the ciclosporin arm of the study had the first episode of ENL recurrence on average 4.1 weeks earlier than those on the prednisolone arm (7.1 versus 11.2 weeks, p=0.114). The difference in median number of weeks to the first episode of ENL recurrence was even greater (4 vs 12 weeks).

More than half of the ENL recurrences in the patients on the ciclosporin arm occurred around week 4. This corresponds to the time in the ciclosporin arm treatment regimen when patients are weaned off the initial prednisolone cover.

The total number of ENL recurrence episodes in the ciclosporin group is also higher (23 versus 20), and although the per-patient rate of ENL flare-up is different for both study arms (2.3 vs. 2), there is no significant difference (p=0.684).

Patients in the ciclosporin arm had many more severe episodes of ENL flare-up during the treatment period (week 0-16), and required 2.5 times more additional prednisolone to control ENL.

Higher rates of minor and major adverse events occurred in patients in the prednisolone arm, as well as in those patients in the ciclosporin arm taking additional prednisolone.

Quality of life scores, assessed by Amharic SF-36, improve for patients with chronic ENL randomized to both study arms, as shown by the increased physical and mental summary components. There was no statistically significant difference in score changes for any of the SF-36 scales for both groups of patients on the two different treatment arms.

7.3 TESTING FOR A POSSIBLE ENL SEVERITY SCALE

Data on ENL features and specialist opinion of severity grading done at each assessment separately were analysed. Patients from both ciclosporin in ENL studies were assessed. A total of 33 patients had 332 assessments done.

ENL symptoms and clinical signs were assessed separately.

Scale reliability

The reliability or internal consistency of the scale was assessed using Cronbach's Alpha, with an α value between 0.7 and 0.9 being considered as acceptable. The contribution of each item in the scale was assessed by calculating Cronbach's α for the scale if that item was removed.

The Cronbach's alpha for ENL symptoms was 0.811. Removal of the following individual items resulted in an increase in the alpha: the degree of malaise, new pain in eyes and new pain in testicles (Table 7.18). This indicates that removal of one or more of these items might improve the remaining items ability to measure the severity of ENL.

Item on ENL symptoms scale	Cronbach's Alpha if Item Deleted
Degree of malaise	0.848
New lumps on skin	0.778
New sensory loss	0.789
New weakness	0.795
New tingling	0.78
New pain in joints	0.768
New pain in bones	0.771
New pain in testicles	0.805
New pain in eyes	0.809
New visual disturbance	0.816

Table 7.18 Cronbach's α for the scale of ENL symptoms when individual item indicated is removed

The Cronbach's alpha for clinical signs of ENL found on examination was 0.784. Removal of the following individual items resulted in an increase in the alpha: the

red eyes, proteinuria and lymphadenopathy (Table 7.19). This indicates that removal of one or more of these items might improve the remaining items ability to measure the severity of ENL. The Cronbach's alpha once the red eyes and proteinuria have been removed was 0.803.

Items on ENL clinical signs scale	Cronbach's Alpha if Item Deleted
Number ENL lesions	0.74
Degree of inflammation in ENL lesions	0.735
Sensory function change	0.768
VMT change	0.777
Nerve tenderness	0.76
Bone tenderness	0.762
Oedema	0.757
Joint swelling/ dactylitis	0.773
Lymphadenopathy	0.783
Testicular tenderness	0.781
Fever	0.775
Proteinuria	0.783
Red eyes	0.799

Table 7.19 Cronbach's α for the scale of ENL clinical signs when individual item indicated is removed

Scoring system

Scores were initially kept separate with presence of symptoms scoring a 1 and absence a 0 out of a total of 9, plus a special 0-5 grade for degree of malaise. The total possible score for ENL symptoms is 14. Each clinical signs was scored between 0 and 4, depending on the range of answers possible (Table 7.20). Red eyes and proteinuria were removed after scale reliability calculations showed that Cronbach's alpha improved if these items are deleted. The total possible score for ENL clinical signs is 23. There was good correlation between scores of the ENL symptoms and ENL clinical signs ($p<0.0001$).

	SCORE 0	SCORE 1	SCORE 2	SCORE 3	Total possible
Number of ENL lesions	0	1-5	6-20	21+	3
Inflammation in the ENL lesions	None	Erythema and pain – function not affected	Erythema and pain – function affected	Erythema and pain – function affected plus ulceration	3
Nerve tenderness	None	Tender on palpation	Withdraws		2
Bone tenderness	None	Tender on palpation	Withdraws		2
Oedema (ankle, face, hands)	None	Present	Gross		2
Joint swelling	None	Present	Affects function		2
Lymph nodes	Normal	Enlarged and tender			1
Testicles	Normal	Tender			1
Fever	Normal	High			1
VMT change	No change	MRC 4	MRC3	MRC<3	3
ST change	No change	One nerve	Two Nerves	≥ nerves	3

Table 7.20 Scoring system used for severity of ENL clinical signs

Discriminant validity

The expert assessment of the severity of the ENLs was categorized as "no active signs of ENL" in 153 assessments, "mild" in 76 assessments, "moderate" in 39 and "severe" in 63.

ENL symptoms

The median scores for ENL symptoms for each category of reaction severity are shown in the box plot in Figure 7.16 with the inter-quartile range (IQR).

Outliers are indicated by either a circle or an asterisk which is labelled with the individuals unique study identifier. A circle indicates a result is 1.5 to 3 times the IQR. An asterisk is a more extreme outlier at > 3 times the IQR.

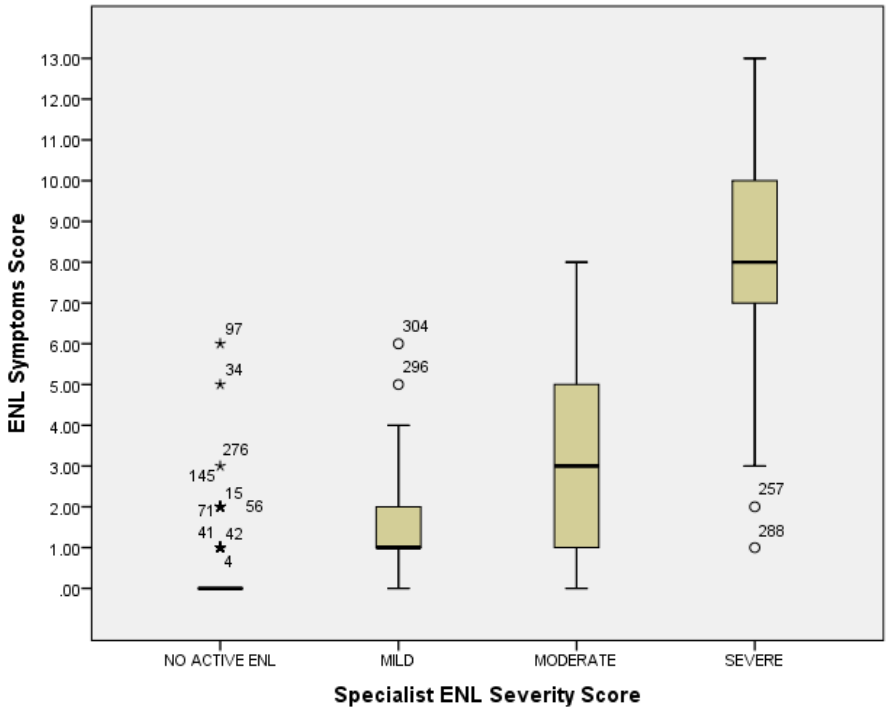


Figure 7.16 Severity score and specialist assessment of severity for ENL symptoms

The median scores for each category were: none =0, (IQR= 0); mild = 1.0 (IQR=1), moderate = 3 (IQR=4) and severe = 8 (IQR=3). The differences between the mild and moderate group and the moderate and severe groups reached statistical significance ($p< 0.0001$ respectively). Analysis of variance to test the ability of the scale to discriminate between different clinical severity categories showed statistical significance of $p<0.0001$.

There are ten extreme outliers in the "no active ENL" category. Looking back at the patient data, these patients had no ENL nodules but the scores were positive because of the presence of other symptoms, possible not related to ENL.

ENL clinical signs

The median scores for ENL symptoms for each category of reaction severity are shown in the box plot in Figure 7.17 with the inter-quartile range (IQR).

The median scores for each category were: none =0, (IQR= 1); mild = 2.0 (IQR=1), moderate = 4 (IQR=3) and severe = 9 (IQR=5). The differences between the mild and moderate group and the moderate and severe groups reached statistical significance ($p< 0.0001$ respectively). Analysis of variance to test the ability of the

scale to discriminate between different clinical severity categories showed statistical significance of $p<0.0001$.

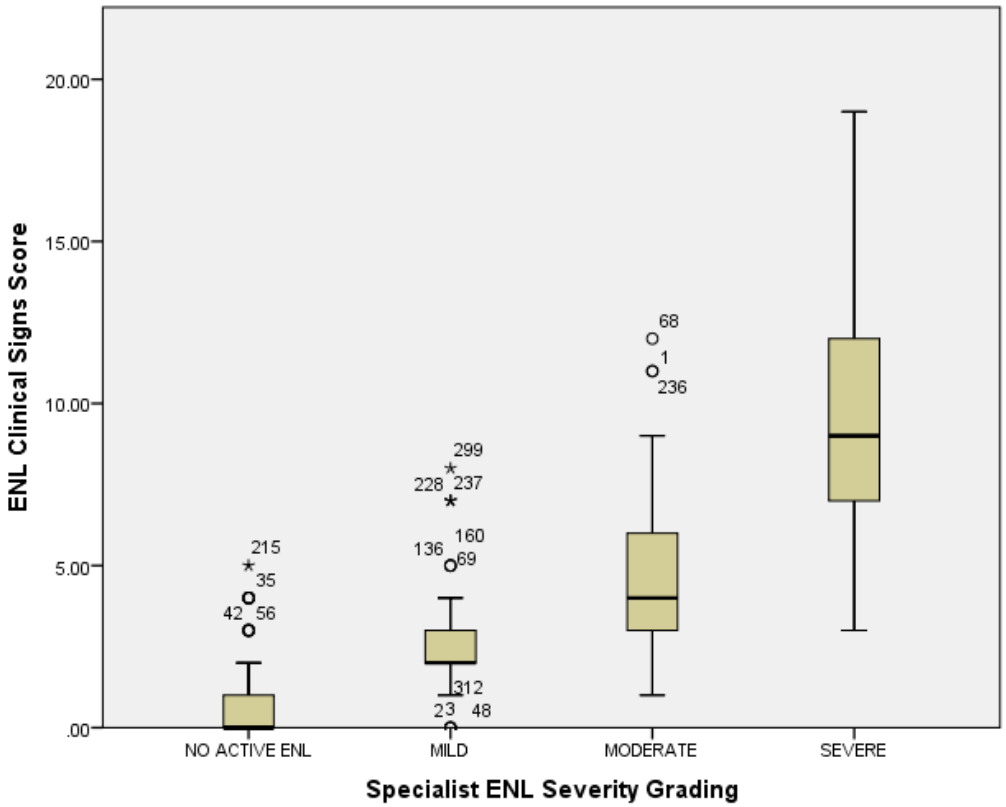


Figure 7.17 Severity score and specialist assessment of severity for ENL clinical signs

Despite an increase in mean score for each level of severity, there was considerable overlap in the range of scores that were derived for both symptoms and clinical signs of ENL.

Determining cut off points for severity

Receiver operating characteristic (ROC) curves can be used to determine cut off points for mild, moderate and severe reactions by calculating the sensitivity and specificity of the scale scores for mild and moderate groups and moderate and severe groups respectively.

ROC curves for the ENL symptoms (Figure 7.18) and clinical signs (Figure 7.19) scale scores was plotted for patients identified as mild or moderate by the specialist

opinion and for those categorized as moderate or severe. This facilitates the determination of cut off scores for each category.

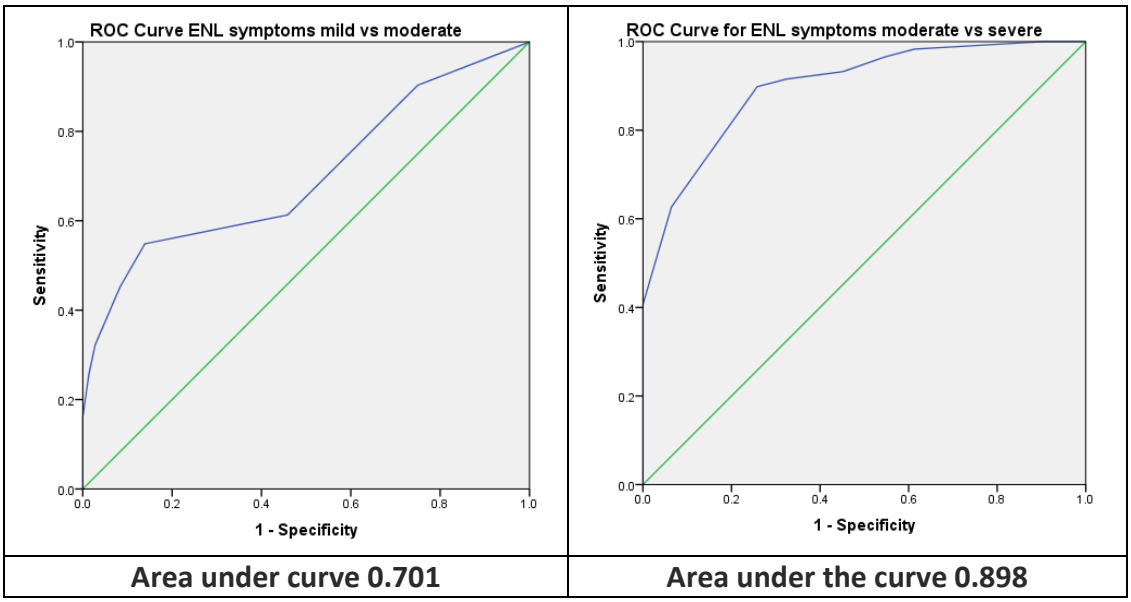


Figure 7.18 ROC curve for ENL symptoms score

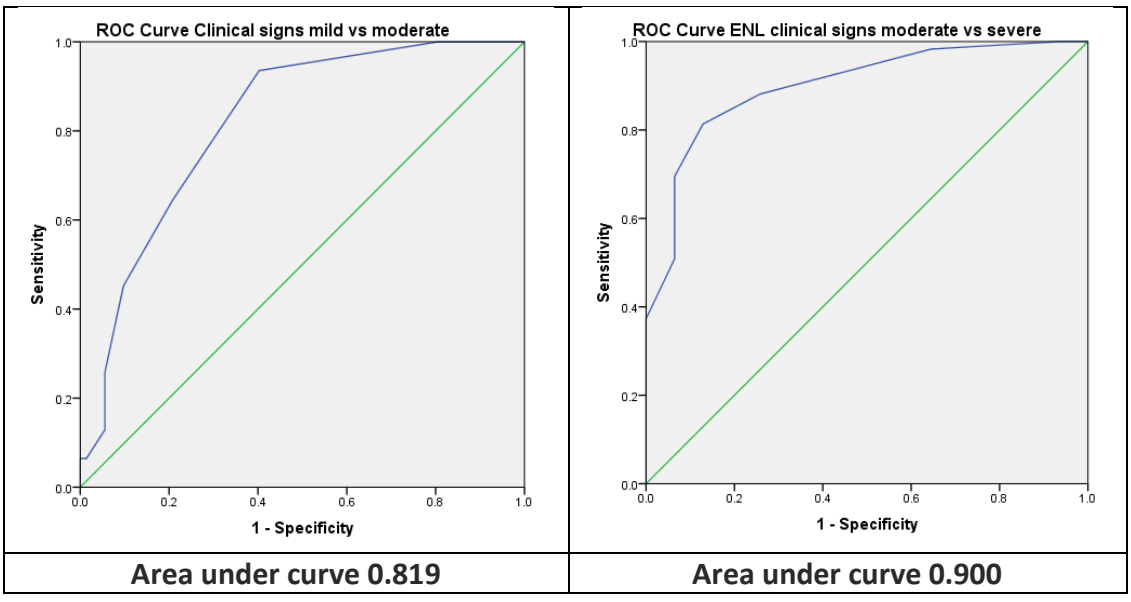


Figure 7.19 ROC curves for ENL clinical signs curve scores

The area under the curves for all four categories were above 0.701 indicating that the scale is a fair discriminator between the severity categories traditionally used by clinicians. Using the ROC curves in conjunction with a consideration of the clinical

meaning of a given score we determined the following cut off points. This was done by choosing scores with a high sensitivity and reasonable specificity (Table 7.21).

Scale grading - ENL symptoms	Scores	Sensiti-vity	1 – Spe-cificity
Mild	1.0000	1.000	1.000
	.5000	1.000	.903
	1.5000	.983	.613
Moderate	2.5000	.966	.548
	3.5000	.932	.452
Severe	4.5000	.915	.323
	5.5000	.898	.258
	6.5000	.763	.161
	7.5000	.627	.065
	8.5000	.407	0.000
	9.5000	.237	0.000
	10.500	.153	0.000
	11.500	.034	0.000
	12.500	.017	0.000
	14.000	0.000	0.000

Scale grading - for ENL signs	Scores	Sensiti-vity	1 – Spe-cificity
Mild	1.0000	1.000	1.000
	2.5000	1.000	.935
	3.5000	.983	.645
Moderate	4.5000	.932	.452
	5.5000	.881	.258
Severe	6.500	.814	.129
	7.500	.695	.065
	8.500	.508	.065
	9.500	.373	0.000
	10.500	.322	0.000
	11.500	.288	0.000
	12.500	.237	0.000
	13.500	.136	0.000
	14.500	.085	0.000
	15.500	.034	0.000
	17.500	.017	0.000
	20.000	0.000	0.000

Table 7.21 Scores and cut off points for symptoms and clinical signs of ENL

In the symptoms score for ENL severity, a mild score is characterised by a score of less than 2. A moderate reaction is a score between 2 and 4, whilst a score above 4 indicated severe ENL. For the clinical signs score for ENL severity, mild is a score under 4, moderate is a score between 4 and 6, and severe is a score of 6 and above.

7.4 DISCUSSION OF CICLOSPORIN IN ENL PILOT STUDIES

1. Clinical outcomes

The 2009 Cochrane review on the management of ENL (van Veen *et al.*, 2009a) found that studies were small and poorly reported and that no clear benefit for interventions could be found from the 13 RCTs selected (van Veen *et al.*, 2009a). Comparison between studies was difficult because of varying outcome measures and reporting on adverse events was limited. None of the studies assessed the effect of the intervention on quality of life in participants.

In these ENL studies we tried to implement a strict methodology selecting outcome measures that are relevant to the patient's well-being and take into account the natural history of ENL.

Of the 33 patients recruited to the two ENL pilot studies, 13 had new ENL and had not previously received prednisolone, whilst 20 patients had recurrent or chronic ENL that had deteriorated whilst on prednisolone. The latter group had on average been on prednisolone for 24 months prior to recruitment, at which time the mean dose of prednisolone was 20mg/day. Few trials in ENL report on the ENL type in participants. In an Indian cohort, acute single episode ENL accounted for only 8% of cases, whereas chronic ENL accounted for 62.5% of (Pocaterra *et al.*, 2006). In Ethiopia, 76% of patients presenting to the leprosy clinic had chronic ENL (Doni & Lambert, 2013), and in field studies, one third of ENL patients developed a chronic condition lasting more than two years (Saunderson *et al.*, 2000a). It is important to try and separate out participants with chronic ENL which is more difficult to treat compared to those with a single episode of acute ENL.

Our study randomization technique was effective as there was no significant difference in age, sex and Ridley-Jopling classification between the patients in both study arms, for the two studies.

At recruitment, 29 out of 33 patients, were graded as having severe ENL by the specialist. Ulcerated ENL nodules occurred in 25% of our cases which is comparable to the 31% of ENL cases in the prospective study of clinical features of ENL in Ethiopia (ENLIST (Doni & Lambert, 2013)). There was no significant difference in

the frequency of extra-cutaneous manifestations of ENL. Bone pain and neuritis were the most common (76%), followed by peripheral oedema (73%). Testicular tenderness was present in 45% of the male patients. Fever, a symptoms often reported in association with ENL was present in only 42% of our participants.

The patients with new ENL (ENLA) randomized to the ciclosporin arm, showed promising results. There was a clear delay of 16 weeks (median 12 vs. 28) in onset of the first ENL recurrence episode; recurrence episodes were fewer and less severe requiring less additional prednisolone to control ENL. The results from this small pilot study suggest that ciclosporin is effective in the management of ENL in individuals experiencing their first episode of ENL.

The natural history of ENL may affect responses in the patients with new ENL. It is difficult to say which of these patients are going to be have a single acute episode only or develop chronic/ recurrent ENL. It may be that the patients with new ENL (both in the ciclosporin and prednisolone arms) who had numerous flare-ups following the first episode would develop chronic/recurrent ENL. The ability to differentiate between patients who develop the different types of ENL might guide future studies better.

The 20 patients with chronic or recurrent ENL (ENLB) showed less benefit from ciclosporin. In comparison to patients in the prednisolone arm, the patients in the ciclosporin arm of this study had the first episode of ENL flare-up on average 8 weeks earlier (median 4 vs 12), with a higher number (23 vs. 20) and higher severity of ENL flare-up episodes necessitating more additional prednisolone to control ENL.

In the design of the study, the drug regimen for the ciclosporin study arm, assumed that four weeks of initial prednisolone would adequately cover the slow onset of action of ciclosporin (Table 7.22). A number of problems can be identified in retrospect with this regimen. The onset of action of ciclosporin is reported to be between four to eight weeks (Sandoz., 1997), so potentially stopping the adjunctive prednisolone at week 4 was too early.

The rate of decrease of prednisolone may also have been too rapid in this group. Clinical experience with ENL patients shows that patients often flare-up as soon as prednisolone is decreased to a certain level or stopped (Pocaterra *et al.*, 2006). Thus patients, in whom chronic ENL would usually be controlled on at least 20mg of

prednisolone, started flaring up when the dose dropped under 20mg. There are no published trials on the rate of decrease in prednisolone for ENL treatment.

Another factor to consider is that patients in the prednisolone arm started at much higher doses of prednisolone (60mg) which was decreased slowly adding a protective effect from ENL recurrence for a longer amount of time (Table 7.22).

	Prednisolone alone	**Ciclosporin and Prednisolone arm**
Week 1	Prednisolone 60mg	Ciclosporin 7.5mg/kg + Prednisolone 40mg
Week 2	Prednisolone 55mg	Ciclosporin 7.5mg/kg + Prednisolone 40mg
Week 3	Prednisolone 50mg	Ciclosporin 7.5mg/kg + Prednisolone 20mg
Week 4	Prednisolone 45mg	Ciclosporin 7.5mg/kg + Prednisolone 10mg
Week 5	Prednisolone 40mg	Ciclosporin 7.5mg/kg
Week 6	Prednisolone 35mg	Ciclosporin 7.5mg/kg
Week 7	Prednisolone 30mg	Ciclosporin 7.5mg/kg
Week 8	Prednisolone 25mg	Ciclosporin 6mg/kg
Week 9	Prednisolone 20mg	Ciclosporin 6mg/kg
Week 10	Prednisolone 20mg	Ciclosporin 6mg/kg
Week 11	Prednisolone 15mg	Ciclosporin 4mg/kg
Week 12	Prednisolone 15mg	Ciclosporin 4mg/kg
Week 13	Prednisolone 10mg	Ciclosporin 3mg/kg
Week 14	Prednisolone 10mg	Ciclosporin 3mg/kg
Week 15	Prednisolone 5mg	Ciclosporin 2mg/kg
Week 16	Prednisolone 5mg	Ciclosporin 1mg/kg

Table 7.22 Treatment regimen for the ENL study

In the ciclosporin arm of ENLB, of the nine patients who had an ENL recurrence, 67% had it at week 4 or before compared to the eight patients in the prednisolone arm where 14% only had a recurrence in that period. This suggests that as soon as prednisolone was stopped, there was a high risk of ENL flare-up either because the ciclosporin's immunosuppressive action was still too low or because prednisolone was decreased too rapidly. Once an ENL flare-up occurs in a patient, total prednisolone is increased to 40 or 60mg depending on the severity, and then gradually decreased by 5mg a week. Delaying the onset of ENL flare-up decreases the total amount of additional prednisolone needed. This could explain why in the patients receiving ciclosporin, patients with chronic ENL needed almost twice as much additional prednisolone than those with acute ENL (Table 7.23).

Mean additional prednisolone	Cn arm new ENL	Cn arm chronic ENL
Intervention period: wk 0-16	850 mg	1780 mg
Follow-up period : wk 17-32	1285 mg	2290 mg
Total study	2135 mg	4070mg

Table 7.23 Additional prednisolone required by patients with acute and chronic ENL on the ciclosporin arm of studies ENLA and ENLB

The patients with chronic or recurrent ENL (ENLB) had been on prednisolone for long periods of time before recruitment (in this group, an average of 2 years). A proportion of individuals with inflammatory conditions such as asthma, rheumatoid arthritis (RA) and inflammatory bowel disease show corticosteroid resistance or insensitivity (Barnes & Adcock, 2009b). Drug tolerance is when a subject's response to a specific drug and drug concentration is progressively reduced, requiring an increase in concentration to achieve the desired effect. Between the rebound effects of prednisolone and a possible build-up of tolerance, it may be very difficult to stop prednisolone in patients with chronic ENL. It is not known how common the phenomena of corticosteroid resistance or tolerance, are in patients with leprosy reactions.

Patients in the ciclosporin arm needed more prednisolone for NFI and neuritis than those in the prednisolone arm. There were some baseline differences between the two groups, with patients on the ciclosporin arm exhibiting more NFI at recruitment. The small numbers of patients, make it difficult to comment on the difference between prednisolone and ciclosporin in their efficacy to treat NFI. The larger T1R trial shows a similar improvement in NFI for both medications, making the baseline difference in nerve function between ENL study groups the stronger contributing factor for the additional prednisolone required for NFI.

2. Adverse events

Minor and major adverse events directly attributable to prednisolone were much more frequent than those attributable to ciclosporin (Table 7.24). This is discussed further in the final chapter of this thesis.

FREQUENCY OF ADVERSE EVENTS ATTRIBUTED TO:		Ciclosporin (17)	Prednisolone (16)
MINOR ADVERSE EVENTS	Moon Face	0	11
	Acne	2	14
	Fungal infections	2	15
	Gastric pain	1	19
	Hypertrichosis	1	0
	Gum hyperplasia	1	0
MAJOR ADVERSE EVENTS	Infections	4	23
	Infected ulcers	3	10
	Hypertension	1	1
	Increased blood sugar/diabetes	0	4
	Nocturia	0	3
	Night sweats	0	2
	Anxiety	0	1
	Depression	0	1

Table 7.24 Number of patients with side effects in both ENL studiesrelated to either prednisolone or ciclosporin

Serious adverse events attributable to prednisolone were also more common.

3. Quality of life

This is the first time that the SF-36 questionnaire has been used in a leprosy clinical trial. Our Amharic translation was validated before using it in the ciclosporin trials.

All the comparisons were done on group mean quality of life scores and not on individual patient scores. There was no statistically significant difference in changes in all scores between patients on the ciclosporin arm and those on the prednisolone arm. In general, both physical and mental scores improved in both study arms in both acute and chronic ENL patients. Interpretation of results was made difficult by the small sample sizes.

It is interesting to note that patients with chronic ENL (ENLB) scored less in the summary scores both at start and end of treatment than those with acute ENL

(ENLA), reflecting how chronic ENL, or its long term treatment, affects quality of life of patients (Figure 7.20).

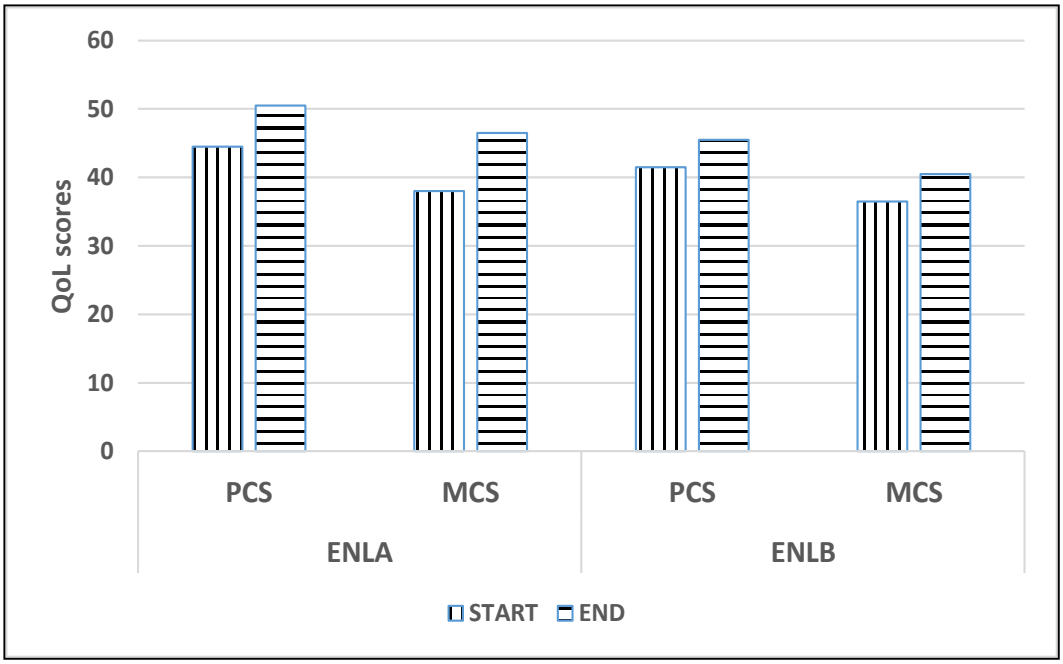


Figure 7.20 SF-36 QOL scores for ENLA and ENLB

The 33 patients with ENL had lower quality of life score than the Ethiopian population norms (Chapter 4), especially in the physical summary component score (43 vs 54) and the mental summary component score (37 vs 49).

In conclusion, ciclosporin shows promising results in the management of acute ENL in this small pilot study. Steroid–sparing effects were not noted for ciclosporin in the management of chronic ENL as steroid tolerance and dependency made interpretation of results more difficult.

4. ENL severity scale

Since the ENL scoring system suggested in section 7.3 of this chapter has not been validated it was not used as an outcome measure for the ciclosporin in ENL clinical trials. The severity grading of ENL was done by specialist opinion.

Categorizing severity into mild, moderate and severe may be the gold standard at present but these are subjective physician determined categories. For the three study physicians involved in the ENL trials, severity grading depended on an undefined combination of number of ENL nodules, inflammation, associated clinical features and depended on many factors including the amount of prednisolone taken by the patient when a flare-up occurred. Neuritis automatically categorised the episode of ENL as severe, in our setting.

The scoring system we designed has two components, symptoms expressed by the patients and clinical signs found by the physician on examination. Reliability (internal consistency) of the scale was good for both symptoms and signs, as shown by the Cronbach's alpha values. Discriminant validity was excellent for both sections of the scale with the analysis of variance proving the ability of the scale to discriminate between different clinical severity categories ($p<0.0001$). Cut off points for severity were determined for both symptoms and signs.

Having a two component score makes it difficult to interpret severity and since the correlation between scores for symptoms and scores for clinical signs was highly significant, it maybe be better to design a grading system based on clinical signs alone. If malaise was thought to be an important feature it would be the only item based on patient history and a way of incorporating this would need to be found. Using Wong-Baker faces to assess malaise in our patient group was straight forward.

Weighting of items was not applied and this is an important part of any scale for severity. Deciding on the importance of each item, and deciding how to score this, is an important part of severity scale development. Another important issue that requires further work is that of determining the Minimally Important Difference (MID) from a patient perspective in scores derived from the scale before and after treatment. This is important because it provides a meaningful patient-centred outcome measure of change. Inter-observer reliability needs to be tested as well before validating a scale in different populations. Intra-observer reliability would be difficult to test in this instance because of the effect of treatment on the signs of ENL.

CHAPTER 8 CONCLUSIONS, REFLECTION & SUMMARY OF FUTURE WORK

1. **Adverse events**
2. **T1R Studies**
3. **T1R Severity Scale**
4. **ENL Studies**
5. **ENL Severity Scale**
6. **Quality of Life assessment tool**
7. **Reflection**
8. **Summary of future work**

This chapter starts with the analysis of adverse events from the combined data of all four ciclosporin/prednisolone clinical trials and is followed by conclusions for each section of this thesis. The reflective section is followed by the summary of future work.

8.1 ADVERSE EVENTS

Combining all four studies together gives us a total number of 120 patients who were exposed to prednisolone and 67 patients who were exposed to ciclosporin. Every patient reported at least one adverse event, whether minor or major.

The differences in frequency of adverse events between patients recruited to either study arms are described in Chapters 6 and 7. We wanted to look at difference in adverse events between the two drugs. The 67 patients in the ciclosporin arm were given prednisolone for 4 weeks at the start of the study and at any other time when a flare-up of reaction occurred. This makes it difficult to tease out which drug has a link with a specific side effect in this group. Three study physicians attempted independently to attribute a causal link between each adverse even and either ciclosporin or prednisolone, depending on whether the patient was receiving additional prednisolone. Results were then compared and differences discussed. Equivocal results were left out of the final tables (less than 20 adverse events), and tables were recombined with adverse events for each drug (Table 8.1.)

As patients were exposed to both drugs it would be inappropriate to calculate odd ratios or risk ratios associated to taking these drugs, in these studies. Any statistically significant conclusions are limited.

The percentage of patients experiencing side effects related to ciclosporin was much lower than those experiencing side effects related to prednisolone. In both groups, infections were the most common side effect: 16 % in the ciclosporin exposed patients and 42 % in the prednisolone exposed patients. As both drugs are immune-suppressants, this is not surprising. Infections include bacterial and viral respiratory tract infections, urinary infections and other systems. As we do not have a non-drug exposed group of patients with whom to compared infection rates in general in this Ethiopian resource-limited setting, it makes it difficult to comment on what

percentage of infections in the study is related to the immune-suppressive effect of the drugs.

Rates of infected ulcers were also high. Ulcers are common in leprosy as patients are prone to pressure related injuries and burns on insensitive hands and feet. Like general infections, it is difficult to attribute all the infected ulcers to immune-suppressing medication. We can however note that proportionately more infected ulcers are linked to patients on prednisolone (42% vs.10%).

Side effect attributable to Ciclosporin	% in 67 pts
Infections	16%
Gastric pain	12%
Hypertension	12%
Infected ulcers	10%
Headache	9%
Hypertrichosis	9%
Gum hyperplasia	9%
Fungal infections	7%
Acne	6%
Night sweats	4%
Sterile dysuria	4%
Diarrhoea	4%
Nocturia	3%
Vomiting	3%
Blurred vision	3%
Depression /anxiety	1%

Side effect attributable to Prednisolone	% in 120 pts
Infections	42%
Infected ulcers	42%
Gastric pain	33%
Fungal infections	23%
Acne	19%
Moon Face	13%
Diarrhoea	7%
Nocturia	5%
Night sweats	3%
Depression /anxiety	3%
Vomiting	3%
Diabetes	2%
GI bleeding	2%
Headache	2%
Blurred vision	2%

Table 8.1 Percentage of patients who experienced adverse events related to ciclosporin or prednisolone

33% of patients had gastric pain attributable to prednisolone and 12% to ciclosporin. Patients in whom gastric pain or dyspepsia was related to H. Pylori were removed from this analysis. GI bleeds occurred in three patients on high doses of prednisolone (2%). There was a three-fold increase in fungal infections attributable to prednisolone (23% vs. 7%), which can be explained by the fact that ciclosporin, a known antifungal, may have offered some protection. Acne, which can occur in

association to both drugs, had a higher frequency in patients on prednisolone (19% vs 6%). Night sweats, nocturia, vomiting, visual disturbances occurred in similar proportions in both groups. Depression and anxiety were more common in the prednisolone group (3% vs. 1%).

Of the serious adverse events, diabetes occurred in 2% (n=3) of cases on prednisolone. Tuberculosis was diagnosed in three patients, one patient was on prednisolone only, whereas two patients were on ciclosporin and prednisolone, with high amounts of additional prednisolone. Two patients died of possible perforated peptic ulcers with multi-organ failure; both were receiving prednisolone only.

Only two clinical trials with ciclosporin in leprosy reaction have been conducted in Ethiopia and Nepal (Marlowe *et al.*, 2007). In Table 8.2, side effect rates in our study are compared to those in the Marlowe study and to the Novartis drug information leaflet for ciclosporin (Table 2.18 and Appendix 3).

Adverse Event	Marlowe study* (n=43)	Drug info leaflet	Our study (n=67)
Hypertension	9%	27-53%	12%
Headache	-	15-25%	9%
Diarrhoea	-	6-12%	4%
Hypertrichosis	-	7-45%	9%
Gum hyperplasia	-	4-16%	9%
Wound and skin infections	-	7%	10%
Fungal infections	-	7%	7%
Other infections	-	5-16%	16%
Increased serum creatinine	14%	20-48%	3%
Gastric pain	5%	6-15%	12%

*(Marlowe *et al.*, 2007)

Table 8.2 Comparison of frequency of ciclosporin side-effects

Comparing the frequency of prednisolone related adverse events in our study to those in other leprosy studies does not allow many conclusions as few studies report adverse events systematically. In the TRIPOD study (Richardus *et al.*, 2003b), 8.4% of Nepali patients experienced a minor adverse event. These patients received a total of either 1.96g or 2.52g of prednisolone. The meta-analysis looking at adverse events during corticosteroid therapy in 93 double-blind randomized controlled trials

analysed the data for 8700 patients had participated (Conn & Poynard, 1994). The mean total dose received was 2.2g over a mean duration of 64 days. In our studies, patients mean total prednisolone received over 20 weeks was 3.8g for patients in T1R and 2.3g for patients in ENL.

Table 8.3 shows the frequency of adverse events of prednisolone in two leprosy reaction clinical trials in which adverse event recording was methodical, in our four studies and in meta-analysis on prednisolone related adverse events.

Adverse Event	**TRIPOD (n=401)** (Richardus *et al.*, 2003b)	**Methylprednisolone study (n=42)** (Walker *et al.*, 2011)	**Other studies**	**Our studies (n=120)**
Acne	2%	23.8%	10-20%*	19%
Moon face	3%	19%	8% **	13%
Fungal infection	1.2%	1%		23%
Gastric pain	18%	16.7%		33%
Nocturia/ polyuria/polydypsia		9.5%		5%
Diabetes	n=3	n=0	4 fold increase ***	n=3

*****(Curtis *et al.*, 2006)**; ****(Fardet *et al.*, 2007)**; *****(Conn & Poynard, 1994)

Table 8.3 Comparison of frequency of prednisolone side-effects

There was no episode of de-novo hypertension associated with prednisolone treatment in our study, as also not seen the TRIPOD and Methylprednisolone studies. The Conn and Poynard meta-analysis found that the frequency of hypertension was increased in patients treated with corticosteroids and that this difference was significant. Psychiatric symptoms were not reported in either the TRIPOD or the Methylprednisolone studies, but occurred in 3% of patients on prednisolone in our study. Three patients complained of anxiety and depression.

None of the patients in the TRIPOD or the Methylprednisolone study were diagnosed with TB during the study. Our three cases of TB may be explained by geographical variation in the incidence of TB between Nepal and Ethiopia. The WHO country profile report states that the annual incidence of TB (all cases including HIV positive) for 2012 for Ethiopia was 247 cases per 100 000, and for

Nepal 163 cases per 100 000 (WHO TB data 2012). The meta-analysis reported five cases of TB in 2056 individuals treated with prednisolone (international literature).

We were unable to examine the effect of prednisolone on bone density, although osteoporosis is a known side effect of prednisolone.

Collecting data on adverse events in a trial setting, with pre-prepared questionnaires and reminders in the clinical examination sheet, reveals higher numbers of side effects than in observational studies.

Large multi-centred trials would more accurately identify the risk of adverse events. The cost of such trials would be high. Another way of getting more data would be to ensure, more regular and systematic collection of adverse events in any leprosy related clinical trials, thus allowing for pooling of data.

Leprosy often occurs in resource-limited settings where patients living in poor condition are at risk of malnutrition and infections, thus increasing the rate of adverse events with any immune-suppressant. Prednisolone, in our study has been linked to a higher number of adverse events. This highlights the importance of searching for an alternative treatment in leprosy reactions.

8.2 T1R STUDIES

T1R are immune-mediated events with inflammation of peripheral nerves and skin. T1R are responsible for a significant proportion of nerve damage in leprosy. Immuno-suppression with prednisolone has been the principal treatment for T1R but up to 40% of patients may not improve, and the rates of adverse events associated with long-term use of prednisolone are high.

This study is the first double-blind RCT assessing ciclosporin, a potent immunosuppressant in the management of T1R. It was preceded by a pilot study assessing ciclosporin in 33 Ethiopian patients and eight Nepali patients in T1R (Marlowe *et al.*, 2007).

In our study, all the patients with new T1R treated with ciclosporin and prednisolone or with prednisolone alone improved in all four Clinical Severity Score components. Skin lesions improved in most patient (94-100%); sensation improved the least (49% of patients on prednisolone only and 66% of patients on ciclosporin and prednisolone). Recurrences of T1R were equally frequent in both treatment arms (85%). These recurrences were treated with additional prednisolone. The patients on the ciclosporin arm of the study received 10% less steroids than those on the prednisolone only arm during the 32 weeks of study.

This study has shown that the steroid-sparing effect of prednisolone is limited. The Marlowe pilot study suggested that ciclosporin may be as efficient as prednisolone in the treatment of T1R. The study designs are different and no additional prednisolone was given in the Marlowe study for T1R or NFI flare-up; the dose of ciclosporin was increased in such cases.

In view of the fewer side effects of ciclosporin compared to prednisolone, ciclosporin could therefore be a useful safe alternative second-line drug for patients with T1R in whom prednisolone is not working, and is causing adverse events. An initial cover with prednisolone for a period of eight weeks would be recommended.

Considering that, despite coming off-patent, ciclosporin is still an expensive medication. Presently a 20 week course of ciclosporin for a patient in the weight

range of 40-49kg, would cost USD 820, compared to a course of prednisolone costing USD 10. This, combined with the unavailability of ciclosporin in most leprosy endemic areas, makes me think that a larger study of ciclosporin in T1R is not needed.

This study has highlighted that corticosteroid treatment for T1R and NFI is sub-optimal even when given in large doses for longer durations. At present, the TENLEP multi-centred RCTs are looking at a 32-week course of prednisolone for NFI (Wagenaar *et al.*, 2012). This would mean a cumulative dose of prednisolone greater than 5mg compared to 3.5mg over 20 weeks recommended by Rao (Rao *et al.*, 2006). The development of more prolonged treatment protocols would require careful monitoring of adverse events and in particular the long term sequelae of corticosteroid therapy.

This study has emphasized the difficulty in switching off leprosy inflammation. There is still a great need for better treatment agents for reactions and nerve damage. Clinical studies in T1R should be accompanied by laboratory based research to investigate the mechanisms of inflammation in T1R, identify patients at risk of recurrences and possibly identify a better agent for the treatment of T1R.

8.3 T1R CLINICAL SEVERITY SCALE

The Severity Scale for leprosy T1R was validated in Ethiopian patients and used in our ciclosporin in T1R trials as an outcome measure to reflect changes with treatment. Although the clinical improvement in patients was well reflected by the decreasing severity score some limitations were noted. These included the effect of old nerve function impairment in artificially raising the score in the absence of active T1R. A way of adjusting the score to take into account the effect of old nerve function impairment needs to be investigated.

The scoring system is not equally weighted. Neurological parameters are more heavily represented. This may reflect the importance of nerve function impairment but may not adequately reflect treatment requirements. A study assessing whether adjusting the weighting would be useful could be carried out in conjunction with a study assessing the minimally important difference (MID) from a patient perspective in scores derived from the scale before and after treatment. This is important because it provides a meaningful patient centred outcome measure of change. This study should be performed in a population in which the scale has been validated. Knowing the magnitude of the change in score required to achieve a MID would facilitate power calculations for clinical trials.

On the practical aspect, our Ethiopian physiotherapists accustomed to doing VMT and ST assessment, found the scoring system confusing at first and the layout of the scoring sheet could possibly be simplified.

Further studies of the Clinical Severity Scale for T1R are warranted to determine its utility in future clinical studies as well as how to report scores in studies to allow easy comparison and pooling of results.

8.4 ENL STUDIES

ENL is a complicated phenomenon. There is still a large gap in our knowledge as we are unable to predict which patients are more at risk of developing ENL, how severely and how long they may be affected by ENL. ENL is often chronic and recurrent in nature. Although most agents may work similarly for controlling the acute symptoms of ENL, prevention of recurrences is far more difficult.

Ciclosporin showed promising results in the management of acute ENL in this small pilot study. It did not appear to have a significant steroid–sparing effects in patients with chronic ENL which may have been due to the prolonged use of steroids in these patients in combination with a too rapid decrease of steroids in patients given ciclosporin.

Further research is needed to determine whether the promising results of ciclosporin in acute ENL can be reproduced on a larger scale. Future studies on ENL should have a more tailored prednisolone regimen for patients with chronic or recurrent ENL who are steroid dependant. An alternative regimen of prednisolone is needed, possibly individualized at 1mg/kg then gradually decreasing more slowly over a period of at least 8 weeks allowing for ciclosporin to take over the immunosuppressive action.

A valuable feature of these studies is that they demonstrate the importance of separating patients with the first ENL episode from those with chronic ENL. In future studies, patients with acute ENL, may benefit from a faster reduction of prednisolone, whereas patients with chronic ENL would require a slower reduction of prednisolone and a more sustained immune-suppression.

There appears to be a large difference in incidence as well as severity of ENL between different parts of the world (Voorend & Post, 2013). The possibility that ENL is less severe in some regions, may influence response to treatment.

An internationally agreed on definition of ENL is essential in order to design high quality multi-centre trials.

8.5 ENL SEVERITY SCALE

Although we were limited by a lack of resources, time and patient numbers to develop and validate a scale for ENL severity for our Ciclosporin in ENL pilot studies, the preliminary work done was valuable. It emphasized the difficulties of a severity grading for such a multifaceted condition such as ENL. It remains an important priority to develop and validate an ENL severity scale to use in clinical trials and which can allow for comparison between trials.

Following the analysis of the large study on clinical features of ENL (ENLIST), an ENL Severity Scale should be developed ideally taking into account following features:

- Number of lesions and degree of inflammation
- Nerve tenderness and nerve function impairment
- Ability to capture new vs. old NFI
- Bone tenderness, arthritis and oedema are important
- Assessment of the importance of various systemic symptoms
- Patient's impression of pain severity and malaise
- Ability to capture the importance of acute, recurrent and chronic ENL
- Reaction treatment at the time of assessment should be taken into account
- "Score" for patients showing no clinical signs of active ENL whilst on treatment should be considered
- Simplified version of the severity scale would be useful for use outside clinical research.

8.6 QUALITY OF LIFE

Quality of life has now become an indispensable outcome measure in many randomized clinical trials and other studies. It provides the patient's voice in measuring health improvement or decline and assessing treatment effectiveness.

Very few leprosy clinical trials have reported quality of life as an outcome. We felt that SF-36 was a good health related quality of life tool to use in our clinical trial.

The difficulty in obtaining the previously translated SF-36 in Amharic from the two authors (Kebede *et al.*, 2004) and (Abera *et al.*, 2010), brought out the importance of publishing tools in the translated language. Articles published about validation of a translated tool, should also publish the translated version for verification and comparison.

After translating the SF-36 into Amharic, following published translation guidelines, it was compared to another validated Amharic quality of life tool, the WHOQOL-BREF. Our sample size of 100 was achieved. The validity and reliability analysis conducted showed that both the Amharic WHOQOL-BREF and the Amharic SF-36, two generic health-related quality of life instruments, are useful for assessing quality of life in leprosy patients in Ethiopia. We found the questions in the SF-36 were easier to understand and better at measuring both physical and psychological components of QOL.

Having trained interviewers filling the questionnaire after establishing rapport with the patients ensured that there was no missing data and that inter-rater reliability scored highly. Using interviewers is essential in populations were literacy rates and levels of education are low.

Although quality of life outcomes are considered useful to incorporate in randomised trials, one study found that only 4.2% of trials reported any quality of life outcomes and even fewer comprehensively reported quality of life data using well-validated, familiar instruments (Sanders *et al.*, 1998). A systematic review of 794 randomised trials undertaken between 2002 and 2008 that reported HRQoL outcomes across a range of medical conditions showed that only 56% of trials provided a rationale for the selected outcome measure, 50% provided an HRQoL hypothesis, 28% provided

information about missing data, and 36% did not discuss the HRQoL findings in the context of the other trial outcomes (Brundage *et al.*, 2011). The review noted that when HRQoL data are reported, variation in the summary statistics used and in the use of summative graphs can cause potential confusion.

One of the difficulties we encountered whilst reviewing published studies on quality of life was that score reporting was not comparable, especially for WHOQOL-BREF, despite published scoring recommendation by the developers of the tool. A systematic review looking at the reporting and interpretation SF-36 outcomes in randomised trials published in 2005, only 10 out of the 52 trials reported all 10 SF-36 scores (Contopoulos-Ioannidis *et al.*, 2009). Reporting inconsistencies can hamper the use of HRQoL data for clinical decision making or development of health policy, and can restrict the application of trial results in clinical practice. The CONSORT Patient-Reported Outcome (PRO) extension was published in 2013, with the aims to improve the reporting of HRQoL outcomes in trials (Calvert *et al.*, 2013)

An important consideration when interpreting quality of life scores especially in a clinical trial is the minimal clinically important changes (MCIC) for SF-36 subscales. The MCICs may vary according to the condition under study and may be different when applied to individual patients or to groups of patients. Without established standards for interpreting the change in HRQoL measures attributed to treatments or interventions, researchers often resort to statistical evaluations to detect a statistically significant difference between two groups, such as treatment versus placebo. Statistically significant differences, however, do not imply that a meaningful or relevant difference has been demonstrated for the individuals enrolled in such trials (Sloan *et al.*, 2002). Since minimal clinically important changes (MCIC) for SF-36 subscales have not been studied in leprosy or other NTD, we utilized the published standards for minimal "clinically and socially relevant" change in group scores as a measure of MCIC at a group level (Ware, 1993). These factors affect the interpretation of our results in the ciclosporin trials and will only be fully adjusted for when more clinical trials in leprosy and in other conditions report on quality of life outcomes and standardization studies are conducted.

One draw-back of SF-36v2 is that it is not a freely available tool, limiting its use in resource poor settings. A free alternative and very similar HRQOL tool to consider would be the RAND MOS SF-36 instrument, an earlier version of the SF-36v2.

Our clinical trials results showed that there was no significant difference in the improvement of quality of life between the two treatment arms for each of our four studies. An interesting finding was that patients with chronic ENL had the lowest scores compared to those with acute ENL, those with T1R, and to the general population norms. Quality of life in these patients is probably severely affected by the chronicity of ENL and the side effect of long term treatments.

We would recommend the use of SF-36 to assess health related quality of life in leprosy clinical studies.

8.7 REFLECTION

This study illustrates the many challenges encountered in running a clinical trial in a low-income setting and in a complicated disease such as leprosy.

Leprosy reactions, both T1R and ENL, are multifaceted conditions which are difficult to measure and to treat. Clinical trials in leprosy reactions are often constrained by small sample sizes, different outcome measures and variable trial reporting, making comparison of data and outcomes difficult. The use of validated tools for outcome measures would improve comparability of results.

We conducted the trials comparing ciclosporin and prednisolone in the management of T1R and ENL following strict GCP guidelines and data was managed with outmost care at all stages. Validated tools such as the Severity Scale for T1R and Amharic SF-36 were used in the outcome measures. Although recruitment rates were lower than expected, I minimized loss to follow-up by offering our trial patients as attentive a service as possible with direct telephone contact when needed. Services at the Leprosy Clinic improved for all patients during the trial and dermatologists at the hospital became more interested in leprosy.

I found that careful follow-up of patients revealed a high number of adverse events related to both prednisolone and ciclosporin. The adverse events related to prednisolone were very frequent, and I feel that in adequately resourced settings, prednisolone would not be used to such an extent regardless of adverse events. This brings out questions of equity in global health issues. Ciclosporin related side effects may have been fewer and less severe, but the need for additional prednisolone to cover reaction recurrences may negate this benefit. Data from this work and that of Marlowe suggest that ciclosporin may not be as efficacious as prednisolone in the treatment acute T1R due to a steroid-sparing effect of only 10%. It may therefore not be appropriate to do further trials of ciclosporin in new T1R. However, the benefits of ciclosporin in patients with chronic T1R who do not respond well to prednisolone or experienced important side effects of prednisolone could be studied further. Ideally, a cheaper and more readily available alternative to ciclosporin should be sought.

An important finding from the pilot studies of ciclosporin in the management of acute ENL is the 14-week delay in the onset of ENL flare-ups in patients on ciclosporin. If ciclosporin does have a protective role against recurrence of ENL, it would reduce steroid requirement drastically. This requires further investigation.

What these studies do highlight is that both T1R and ENL are not fully controlled by prednisolone, a drug with many side effects. The search for a better agent to control leprosy reactions, and limit nerve damage, needs to continue.

8.8 SUMMARY OF FUTURE WORK

Scales

- The Clinical Severity Scale for T1R should have the minimally important difference (MID) determined and a method of correcting for old nerve function impairment in the score should be investigated. This is especially important if it is being used as an outcome measure in therapeutic trials. Result reporting should also be standardised to allow for cross study comparison and pooling of data.
- An ENL severity scale needs to be developed with a multi-centre approach and be internationally validated for future use. The results of the on-going prospective study on the clinical features of ENL (ENLIST) should be taken into account.
- Studies investigating the minimal clinically important changes in quality of life scores for leprosy reactions would help in interpreting results and further validate the use of HRQoL outcome measures in leprosy clinical trials.

Future trials

Future clinical trials assessing treatments for leprosy reactions are urgently needed.

- Ciclosporin in new ENL to assess whether the delay in recurrence can be reproduced.
- Ciclosporin compared to prednisolone in patients with chronic T1R.
- Other agents in ENL: methotrexate, biological agents such as infliximab or etanercept
- Other agents in T1R which can replace prednisolone or have a good steroid sparing effect need to be investigated.

Our results from the prednisolone only arm, may be usefully pooled together with those of other studies to get a clearer picture of prednisolone's efficacy in different populations.

Trial requirements

- Leprosy trials should be multi-centred to ensure adequately powered RCTs and should follow current recommendations for design and reporting.
- Evidence based, strict criteria for prescribing additional steroids to individuals with worsening T1R, NFI or ENL, especially when amount of additional steroids is one of the outcome measures when looking for a steroid-sparing drug.
- Outcome measures such as frequency of recurrences and time to next episode of reaction need to be included.
- Longer than three months follow-up to allow realistic investigation into recurrences
- Adverse events should be systematically enquired about and recorded to get a true picture of their frequency.
- Laboratory studies should be done in conjunction with clinical trials to understand the pathophysiology of reactions and guide future treatment options.
- Validated severity scales for T1R and ENL should be used
- Quality of life assessments during clinical trials provide a different window into patient outcomes and should be included in trials, with complete reporting of results and standardised interpretation.

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APPENDIX

APPENDIX 1: CLINICAL SEVERITY SCALE FOR T1RS

	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions	None	Erythema	Erythema + raised	Ulceration	
A2	Number of raised and/ or inflamed lesions	0	1-5	6-10	>10	
A3	Peripheral oedema due to reactions	None	Minimal	Visible but not affecting functions	Oedema affectting function	
A SCORE						

	HANDS	**Purple 2g Monofilament scores**				**Orange 10g Monofilament score**			**Score**
	Nerves	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	
B1	Rt Trigeminal	Felt						Not felt	
B2	Lt Trigeminal	Felt						Not felt	
B3	Rt Ulnar	All sites felt	1 sites not felt	2 sites not felt	3 sites not felt	1 sites not felt	2 sites not felt	3 sites not felt	
B4	Lt Ulnar	All sites felt	1 sites not felt	2 sites not felt	3 sites not felt	1 sites not felt	2 sites not felt	3 sites not felt	
B5	Rt Median	All sites felt	1 sites not felt	2 sites not felt	3 sites not felt	1 sites not felt	2 sites not felt	3 sites not felt	
B6	Lt Median	All sites felt	1 sites not felt	2 sites not felt	3 sites not felt	1 sites not felt	2 sites not felt	3 sites not felt	
	FEET	**Orange 10g Monofilament score**				**Pink 300g Monofilament score**			**Score**
	Nerves	0	0.5	1	1.5	2	2.5	3	
B7	Rt. Post. tibial	All sites felt	1 sites not felt	2 sites not felt	3 sites not felt	1 sites not felt	2 sites not felt	3 sites not felt	
B8	Lt. Post. tibial	All sites felt	1 sites not felt	2 sites not felt	3 sites not felt	1 sites not felt	2 sites not felt	3 sites not felt	
B SCORE									

	Nerves	**0**	**1**	**2**	**3**	**Score**
C1	Rt. Facial	MRC=5	MRC=4	MRC=3	MRC<3	
C2	Lt. Facial	MRC=5	MRC=4	MRC=3	MRC<3	
C3	Rt. Ulnar	MRC=5	MRC=4	MRC=3	MRC<3	
C4	Lt. Ulnar	MRC=5	MRC=4	MRC=3	MRC<3	
C5	Rt. Median	MRC=5	MRC=4	MRC=3	MRC<3	
C6	Lt. Median	MRC=5	MRC=4	MRC=3	MRC<3	
C7	Rt. Radial	MRC=5	MRC=4	MRC=3	MRC<3	
C8	Lt. Radial	MRC=5	MRC=4	MRC=3	MRC<3	
C9	Rt. Lateral Popliteal	MRC=5	MRC=4	MRC=3	MRC<3	
C10	Lt. Lateral Popliteal	MRC=5	MRC=4	MRC=3	MRC<3	
C SCORE						

Total Score	**Score of A + B + C**	

APPENDIX 2: PREDNISOLONE DRUG INFORMATION SHEET

From FDA drug information website http://www.drugs.com/pro/prednisone.html

Classification:

- Adrenal Agents
- Antiinflammatory Agents
- Biologic Response Modifiers
- Corticosteroids
- Hormones and Hormone Modifiers
- Immunosuppressives
- Musculoskeletal Agents

Description, Mechanism of Action, Pharmacokinetics

Description: Prednisone is the most commonly-prescribed oral corticosteroid. The drug is metabolized in the liver to its active form, prednisolone. Relative to hydrocortisone, prednisone is roughly 4 times as potent as a glucocorticoid. Prednisone is intermediate between hydrocortisone and dexamethasone in duration of action. Prednisone is used in many conditions, including allograft rejection, asthma, systemic lupus erythematosus, and many other inflammatory states. Prednisone has very little mineralocorticoid activity, so it is not used in the management of adrenal insufficiency unless a more potent mineralocorticoid is administered concomitantly. Prednisone was first approved by the FDA in 1955.

Mechanism of Action: Glucocorticoids are naturally occurring hormones that prevent or suppress inflammation and immune responses when administered at pharmacological doses. At a molecular level, unbound glucocorticoids readily cross cell membranes and bind with high affinity to specific cytoplasmic receptors. This binding induces a response by modifying transcription and, ultimately protein synthesis to achieve the steroid's intended action. Such actions may include: inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, and suppression of humoral immune responses. Some of the net effects include reduction in edema or scar tissue, as well as a general suppression in immune response. The degree of clinical effect is normally related to the dose administered. The antiinflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, collectively called lipocortins. Lipocortins, in turn, control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of the precursor molecule arachidonic acid. Likewise, the numerous adverse effectsrelated to corticosteroid use are usually related to the dose administered and the duration of therapy.

Pharmacokinetics: Prednisone is rapidly absorbed across the GI membrane following oral administration. Peak effects can be observed after 1—2 hours. The circulating drug binds extensively to the plasma proteins albumin and transcortin, with only the unbound portion of a dose active. Systemic prednisone is quickly distributed into the kidneys, intestines, skin, liver and muscle. Corticosteroids distribute into the breastmilk and cross the placenta. Prednisone is metabolized by the liver to the active metabolite prednisolone, which is then further metabolized to inactive compounds. These inactive metabolites, as well as a small portionof unchanged drug, are excreted in the urine. The plasma elimination half-life is 1 hour whereas the biological half-life of prednisone is 18—36 hours.

Indications

- acute lymphocytic leukemia (ALL)
- acute respiratory distress syndrome (ARDS)
- Addison's disease
- adrenal hyperplasia
- adrenocortical insufficiency
- allergic conjunctivitis
- amyloidosis†
- angioedema
- ankylosing spondylitis
- anterior segment inflammation
- asthma
- atopic dermatitis
- autoimmune hepatitis†
- Behcet's syndrome†
- berylliosis
- bone pain†
- bursitis
- carpal tunnel syndrome†
- chorioretinitis
- chronic lymphocytic leukemia (CLL)
- corneal ulcer
- Crohn's disease
- dermatitis
- dermatomyositis†
- endophthalmitis†
- epicondylitis
- erythroblastopenia
- gout
- gouty arthritis
- graft-versus-host disease
- headache
- hemolytic anemia
- iritis
- juvenile rheumatoid arthritis (JRA)
- keratitis
- kidney transplant rejection prophylaxis
- Loeffler's syndrome
- lupus nephritis
- mixed connective tissue disease†
- multiple myeloma
- myasthenia gravis
- mycosis fungoides
- nephrotic syndrome
- optic neuritis
- osteoarthritis
- pemphigus
- pericarditis†
- pneumonia†
- pneumonitis
- polyarteritis nodosa†
- polychondritis†
- polymyositis
- psoriasis
- rheumatic carditis
- rheumatoid arthritis
- sarcoidosis
- severe pain
- Stevens-Johnson syndrome
- systemic lupus erythematosus (SLE)
- temporal arteritis†
- tenosynovitis
- thrombocytopenia
- thyroiditis
- tuberculosis

- Hodgkin's disease
- hypercalcemia
- hypoplastic anemia
- idiopathic thrombocytopenic purpura (ITP)
- ulcerative colitis
- urticaria
- uveitis
- Wegener's granulomatosis†

†non-FDA-approved indication

Dosage

Equivalent Glucocorticoid dosages. These are general approximations and may not apply to all diseases or routes of administration.

Equivalent glucocorticoid dosages:

Cortisone--25 mg
Hydrocortisone--20 mg
Prednisolone--5 mg
Prednisone--5 mg
Methylprednisolone--4 mg
Triamcinolone--4 mg
Dexamethasone--0.75 mg
Betamethasone--0.6 mg

For maintenence therapy (i.e., replacement therapy) o= f primary (Addison's disease) or secondary adrenocortical insufficiency:

Oral dosage:

Adults: Prednisone 5 mg PO in the AM, and 2.5 mg PO in the PM. Hydrocortisone and cortisone are the preferred agents for these conditions; prednisone has little to no mineralocorticoid properties. For acute conditions, parenteral therapy is recommended initially.
Children: Prednisone 4—5 mg/m2 PO 1—4 times per day. Hydrocortisone and cortisone are the preferred agents for these conditions; prednisone has little to no mineralocorticoid properties. For acute conditions, parenteral therapy is recommended initially.

For the treatment of congenital adrenal hyperplasia (NOTE: hydrocortisone is the preferred glucocorticoid in infants):

Oral dosage:

Adults: 2.5—5 mg PO once daily at bedtime.
Children: 12—13 mg/m2/day PO administered in 2—3 divided doses.

For kidney transplant rejection prophylaxis:

Oral dosage:

Adults: Dosage is titrated to response. Usual dosage ranges from 5—30 mg PO once daily.
For acute graft-versus-host disease prophylaxis in recipients of a allogeneic bone marrow transplant:

Oral dosage:

Adults: 1—2 mg/kg/day PO administered in divided doses.[531]

For palliative management of lymphocytic leukemia:
for palliative management of acute lymphocytic leukemia (ALL):

Oral dosage:

Adults: 40—50 mg/sq.m. PO once daily indefinitely.
•for palliative management of chronic lymphocytic leukemia (CLL) in combination with chlorambucil:

Oral dosage:=

Adults: 80 mg (prednisone) PO once daily on days 1—5. Adm= inister every 2 weeks. OR: 1 mg/kg/day PO on days 1—7, then 0.5 mg/k= g/day PO on days 8—14, then DC. Repeat cycle every 6 weeks.

For the short-term treatment of hypercalcemia secondary to neoplastic disease:

Oral dosage:

Adults: 50—100 mg/day PO for 3—5 days are usually effective in controlling hypercalcemia due to hematologic cancers, lower doses may be effective in some tumor types.[532]

For the treatment of multiple myeloma in combination with an alkylating agent:

Oral dosage:

Adults: 25—60 mg/m2 PO per day for 4 to 7 days; administered in combination with the appropriate dosage regimen of an alkylating agent. This cycle is repeated every 4 to 6 weeks. NOTE: Other multi-drug regimens that include prednisone have been used.

For the treatment of inflammatory bowel disease:
•for short-term treatment of acute exacerbations of Crohn's disease:

Oral dosage:

Adults: Therapy with corticosteroids in the treatment of Crohn's disease is more effective for small-bowel involvement than for colonic involvement Because of the potential complications of steroid use in this disease, steroids should be used selectively and in the lowest dose possible. Therapy is usually started at 40—60 mg/day PO. Adjust the dose based on response. Although there is no evidence that maintenance therapy prevents recurrences, a substantial percentage of patients will require chronic, low-dose (e.g., 5—15 mg/day) therapy.
•for short-term treatment of acute exacerbations of ulcerative colitis:

Oral dosage:

Adults: Therapy is usually started at doses of 40—60 mg/day PO which have been shown to be superior to 20 mg/day PO. Maximum daily dosage is 1 mg/kg/day PO. Improvement is usually noted after 7—10 days. The dose is then tapered over the next 2—3 months and discontinued. Once clinical remission is achieved, corticosteroid therapy should be discontinued since there is no evidence that maintenance therapy prevents recurrences.

For the treatment of serious manifestations of Behcet's syndrome†:

Oral dosage:

Adults: A dosage of 1 mg/kg PO once daily is recommended in internal medicine texts.

For the treatment of rheumatic conditions such as rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), severe psoriasis and psoriatic arthritis, ankylosing spondylitis, acute and subacute bursitis, acute non-specific tenosynovitis, acute gouty arthritis and gout, osteoarthritis, or epicondylitis:

Oral dosage:

Adults: Dosage is titrated to response. Usual dosage ranges 5—30 mg PO once daily.
Children: 0.05—2 mg/kg/day PO in 1—4 divided doses.

For adjunctive therapy in the treatment of carpal tunnel syndrome†:
NOTE: The definitive treatment for median-nerve entrapment is surgery. Corticosteroids are temporary measures; patients who have intermittent pain and paresthesias without any fixed motor-sensory deficits may respond to conservative therapy.

Oral dosage:

Adults: 20 mg PO daily for 2 weeks, followed by 10 mg PO daily for an additional 2 weeks, has provided relief.

For the treatment of selected cases of collagen disorders and mixed connective tissue disease†:
•for the treatment of systemic lupus erythematosus (SLE):
Oral dosage:
Adults: Doses of prednisone for the treatment of various manifestations of SLE vary widely. Doses can range from as low as 5—10 mg/day for maintenance therapy to as high as 1—2 mg/kg/day PO once daily for more acute situations.
• for the treatment of lupus nephritis† in combination with cytotoxic agents (e.g., azathioprine, cyclophosphamide, chlorambucil):
Oral dosage:
Adults: Low to intermediate doses of prednisone (e.g., 0.25 mg/kg/day) are usually adequate for patients with mesangial or mild focal proliferative glomerulonephritis.[997] In patients with diffuse proliferative or severe focal proliferative glomerulonephritis, doses of 1 mg/kg/day for 2 months followed by a gradual tapering have been recommended.[997] In combination with azathioprine or cyclophosphamide, doses of 60 mg PO once daily have been used. Prednisone should be tapered over a 6 month period to 30—60 mg once every other day.[213] In a comparison of oral prednisone and cytotoxic agents, prednisone was inferior to cytotoxic agents in ability to prevent decline in renal function. In this study, prednisone was dosed at 1 mg/kg/day for the first 4—8 weeks, followed by gradual tapering as tolerated.[670] Some clinicians believe that chronic renal failure is cause to discontinue therapy since serum creatinine concentrations > 3—4 mg/dL suggest limited probability of reversibility.[213]
•for the treatment of systemic dermatomyositis† (polymyositis†) in combination with azathioprine:
Oral dosage:
Adults: Initially, large doses of prednisone are used (e.g., 60 mg PO once daily), once the muscle disease is controlled, prednisone should be tapered to 5—10 mg PO every other day.[213]
•for the treatment of nonrheumatic† or rheumaticcarditis, polymyalgia rheumatica†, polyarteritis nodosa†, relapsing polychondritis†, temporal arteritis†, or vasculitis†:
Oral dosage:
Adults: Dosage is titrated to response. Usual dosage ranges 5—30 mg PO once daily (range 5—60 mg PO daily, depending upon disease being treated). Drug can be administered in 1—4 divided doses. Depending on the indication for use, the initial dose may be gradually tapered after 1—2 weeks and discontinued by 4—6 weeks, as guided by the patient's symptoms.
Children: 0.05—2 mg/kg/day PO in 1—4 divided doses.

For the treatment of Wegener's granulomatosis† in combination with cyclophosphamide:
Oral dosage:
Adults: Initially, 15 mg PO four times per day in combination with cyclophosphamide. After 5—7 days, dose should be tapered to single daily dose, then to alternate day therapy; prednisone should be totally discontinued after 4—8 weeks.[213]

For the treatment of autoimmune hepatitis†:
Oral dosage:
Adults: Initially, a dose of 20—30 mg PO once daily has been recommended for autoimmune hepatitis. Some physicians elect to begin therapy with a combination of prednisone and azathioprine. For maintenance therapy, prednisone doses of 5—15 mg PO once daily have been recommended.[1164]

For the treatment of primary amyloidosis† not associated with familial Mediterranean fever:
Oral dosage:
Adults: A 1997 study demonstrated superior results with a combination of melphalan and prednisone than with colchicine alone in the treatment of primary amyloidosis. In this study, prednisone was dosed as 0.8 mg/kg PO once daily for 1 week (e.g., 7 days) every 6 weeks.[1366]

For the treatment of other systemic autoimmune conditions such as acquired hemolytic anemia, congenital hypoplastic anemia, mycosis fungoides, pemphigus, symptomatic sarcoidosis, or nonsuppurative thyroiditis:
Oral dosage:
Adults: Dosage is titrated to response. Usual dosage ranges 5—30 mg PO once daily.

For the treatment of asthma:
•for the treatment of a moderate-severe asthma exacerbation in the emergency department or the hospital:
Oral dosage:
Adults: The National Asthma Education and Prevention Program Expert Panel recommends 120—180 mg/ day PO in 3—4 divided doses for 48 hours, then 60—80 mg/day PO until the peak expiratory flow (PEF) reaches 70% of predicted or personal best.[1515]
Children: The National Asthma Education and Prevention Program Expert Panel recommends 1 mg/kg PO every 6 hours for 48 hours, then 1—2 mg/kg/day (max: 60 mg/day) PO in 2 divided doses until peak expiratory flow (PEF) reaches 70% of predicted or personal best.[1515]
•for the treatment of an acute asthma exacerbation on an outpatient basis in selected patients:
Oral dosage:
Adults: The National Asthma Education and Prevention Program Expert Panel recommends 40—60 mg PO as a single dose or in 2 divided doses for 3—10 days.[1515]
Children: The National Asthma Education and Prevention Program Expert Panel recommends 1—2 mg/kg/day (max: 60 mg/day) PO as a single dose or in 2 divided doses for 3—10 days.[1515]
•for long-term prevention of symptoms in severe persistent asthma:
Oral dosage:
Adults and children: The National Asthma Education and Prevention Program Expert Panel recommends 7.5—60 mg PO administered once daily in the morning or every other day (alternate day therapy may produce less adrenal suppression). Taper to the lowest effective dose. If prednisone is administered once daily, one study indicates that it may be more effective to give the dose in the afternoon at 3:00 pm, with no increase in adrenal suppression.[1943]

For the treatment of thrombocytopenia:
•in patients = with chronic idiopathic thrombocytopenic purpura (ITP):
Oral dosage:
Adults: 1 mg/kg PO once daily has been recommended as a typical initial dosage[533] however, lower doses of 5—10 mg/day PO are preferable for long-term treatment.[1342]
•for the treatment of autoimmune thrombocytopenia associated with SLE:
Oral = dosage:
Adults and children: A comparative study revealed that prednisone in doses of 0.25 mg/kg/day were as effective as higher doses of 1 mg/kg/day.[997]

For the treatment of acute, severe urticaria or angioedema associated with systemic symptoms in patients who fail to respond to epinephrine or histamine blockers including angioedema associated with ACE inhibitor therapy:
Oral dosage:
Adults: Short courses of 30—50 mg/day can be given PO during the late phase of an acute reaction.[570]

For the treatment of myasthenia gravis in patients who are poorly controlled with cholinesterase inhibitor therapy:
Oral dosage:
Adults: Initiate therapy with 15—20 mg/day PO. Increase by 5 mg every 2—3 days as needed up to a maximum of 60 mg/day PO. Then change to every other day therapy.[540]

For the treatment of idiopathic or viral pericarditis†:
Oral dosage:
Adults: 20—80 mg PO once daily. NOTE: Use of corticosteroids are contraindicated in pericarditis after myocardial infarction; corticosteroids retard myocardial scar formation and the incidence of rupture may increase.

For the treatment of nephrotic syndrome:
Oral dosage:
Adults: 40—80 mg/day PO until urine is protein-free, then slowly taper as indicated. Some patients may require long-term dosing.
Children: 2 mg/kg/day or 60 mg/m2/day (maximum 80 mg) PO once daily until urine is protein-free for 3 consecutive days (maximum 28 days). Then 1—1.5 mg/kg or 40 mg/m2 PO every other day for 4 weeks. If needed, the long-term maintenance dose is 0.5—1 mg/kg PO every other day for 3—6 months.[1944]

For the treatment of Stevens-Johnson syndrome:
Oral dosage:
Adults: NOTE: Use of corticosteroids in the treatment of Stevens-Johnson syndrome is controversial.[534] Hydrocortisone equivalents of 240—1000 mg/day have been recommended, however, administration of high-dose corticosteroids have been associated with decreased survival.[535] (Prednisone doses of 60—250 mg/day are equivalent to hydrocortisone doses of 240—1000 mg/day.)

For adjunctive treatment in selected cases of pnuemonia† or pneumonitis:
•for adjunctive treatment of AIDS-associated Pneumocystis carinii pneumonia† (PCP):
Oral dosage:
Adults: For adjunctive treatment in acute AIDS-associated Pneumocystis carinii pneumonia (PCP), give 40 mg PO twice daily for 5 days, then 40 mg PO daily for 5 days, then 20 mg PO daily for 11 days, during anti-infective therapy. In such cases, prednisone should be started within 24—72 hours of the initiation of anti-infective therapy for PCP. Use of corticosteroids in this manner is associated with improved outcomes in patients with PCP.
Children: Safe dosage has not been established.
•for adjunctive treatment of aspiration pneumonitis:
Oral dosage:
Adults: 5—60 mg PO daily. Drug can be administered in 1—4 divided doses. The initial dose may be gradually tapered after 1—2 weeks and discontinued by 4—6 weeks, as guided by the patient's symptoms.
Children: 0.14—2 mg/kg PO daily or 4—60 mg/m2 PO daily, given in 4 divided doses. The initial dose may be gradually tapered after 1—2 weeks and discontinued by 4—6 weeks, as guided by the patient's symptoms.

For the systemic treatment of ophthalmic inflammatory conditions such as endophthalmitis†, optic neuritis, allergic conjunctivitis, keratitis, allergic corneal ulcers, iritis, chorioretinitis, anterior segment inflammation, uveitis, choroiditis, sympathetic ophthalmia (NOTE: Topically applied corticosteroids are as effective as systemic corticosteroids for anterior ocular inflammation):
Oral dosage:
Adults: 5—60 mg PO daily, depending upon disease being treated. Drug can be administered in 1—4 divided doses.
Children:
0.14—2 mg/kg PO daily or 4—60 mg/m2 PO daily, given in 4 divided doses.

For the short-term treatment of acute, severe headache:
Oral dosage:
Adults: 80 mg PO per day for several days.[351] Taper rapidly.

For the adjunctive management of severe pain associated with bone pain†, brain metastases and epidural spinal cord compression:
Oral dosage:
Adults:
10—50 mg/day PO has been used for the management of bone pain. A dosage range of 40—80 mg/day PO has been suggested for the management of spinal cord compression.[1171]

For the treatment of the acute respiratory distress syndrome (ARDS) in patients with sever e disease and no signs of improvement 7—14 days after onset of the condition:
Oral dosage:
Adults: Use of corticosteroids in ARDS is controversial. In patients with severe disease and no signs of improvement, Kollef et al recommend a prednisone-equivalent dose of 2—4 mg (prednisone)/kg/day for 7—14 days.[564] They recommend that corticosteroids not be used in patients at risk of ARDS (i.e., for prophylaxis) or in patients during the first several days of the disease. They also recommend that corticosteroids not be used routinely during the latter phase of the disease unless there is no sign of improvement.

For the treatment of other conditions not listed above including atopic dermatitis, Loeffler's syndrome, berylliosis, erythroblastopenia, or trichinosis:
Oral dosage:
Adults: 5—60 mg PO daily, depending upon disease being treated. Drug can be administered in 1—4 divided doses. Depending on the indication for use, the initial dose may be gradually tapered after 1—2 weeks and discontinued by 4—6 weeks, as guided by the patient's symptoms.
Children: 0.14—2 mg/kg PO daily or 4—60 mg/m2 PO daily, given in 4 divided doses. Depending on the indication for use, the initial dose may be gradually tapered after 1—2 weeks and discontinued by 4—6 weeks, as guided by the patient's symptoms.

For the treatment of tuberculosis† meningitis or pulmonary tuberculosis† controlled by appropriate antituberculosis chemotherapy:
Oral dosage:
Adults: 5—60 mg PO daily, depending upon disease being treated. Drug can be administered in 1—4 divided doses. For tuberculosis meningitis, many experts recommend the use of corticosteroids in stage 2 (confusion or the presence of focal neurological defects) or stage 3 (stuporous or dense paraplegia or hemiplegia) disease, beginnning with prednisone 60—80 mg PO once daily. Alternatively, initial doses of 0.5—1 mg/kg/day PO have been used in patients with stage 1, 2, or 3 tuberculosis meningitis.[1945] The initial dose may be gradually tapered after 1—2 weeks and discontinued by 4—6 weeks, as guided by the patient's symptoms.
Children: 0.14—2 mg/kg PO daily or 4—60 mg/m2 PO daily, given in 4 divided doses.

For palliative management of Hodgkin's disease in combination with antineoplastic agents:

•for palliative management of Hodgkin's disease in combination with mechlorethamine, vincristine, vinblastine, and procarbazine (MVVPP chemotherapy regimen):
Oral dosage:
Adults: 40 mg/m2 PO on days 1—22, then taper. Chemotherapy cycle is repeated every 57 days.
•for palliative management of Hodgkin's disease in combination with mechlorethamine, vincristine, procarbazine, doxorubicin, bleomycin, and vinblastine (MOPP/APB chemotherapy regimen):
Oral dosage:
Adults: 40 mg/m2 PO on days 1—14. Chemotherapy cycle is repeated every 28 days.

Maximum Dosage Limits:
Dosage must be individualized and is highly variable depending on the nature and severity of the disease, and on patient response. Although there is no absolute maximum dosage, the Boston Collaborative Drug Study found that psychiatric events occurred in fewer than 1% of patients when prednisone was prescribed in doses of 30 mg/day or less, whereas the incidence rose to 18% in patients receiving 80 mg/day.[243]

Patients with hepatic impairment:
Specific guidelines for dosage adjustments in hepatic impairment are not available; prednisone is converted to prednisolone, the active moeity, by the liver. The use of oral prednisolone instead of oral prednisone may be preferred in patients with significant hepatic dysfunction (see Prednisolone monograph); dosages are considered equivalent (i.e., 1 mg prednisone is equivalent to 1 mg of prednisolone).

Patients with renal impairment:
Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

†non-FDA-approved indication

Administration Guidelines
NOTE: Dosage must be individualized and is highly variable depending on the nature and severity of the disease, and on patient response. If therapy is continuous for more than several days, withdrawal should generally be gradual.

Oral Administration
•*All oral dosage forms:* Administer with meals to minimize indigestion or GI irritation. If given once daily or every other day, administer in the morning to coincide with the body's normal cortisol secretion.
•*Oral solution or syrup:* Administer using a calibrated measuring device= for accurate measurement of the dose.

Contraindications/Precautions

- *abrupt discontinuation*
- breast-feeding
- cataracts
- children
- coagulopathy
- *Cushing's syndrome*
- diabetes mellitus
- diverticulitis
- *fungal infection*
- GI disease
- glaucoma
- heart failure
- hepatic disease
- herpes infection
- hypertension
- hypothyroidism
- infection
- inflammatory bowel disease
- *measles*
- myasthenia gravis
- myocardial infarction
- osteoporosis
- peptic ulcer disease
- psychosis
- renal disease
- seizure disorder
- surgery
- thromboembolic disease
- tuberculosis
- ulcerative colitis
- vaccination
- *varicella*
- viral infection
- visual disturbance

• Absolute contraindications are in italics.
The manufacturers state that prednisone is contraindicated in patients with systemic *fungal infection*, but many clinicians believe that corticosteroids can be administered to patients with any type of known infection as long as appropriate antifungal therapy is administered simultaneously.

Corticosteroid therapy can mask the symptoms of infection and should not be used in cases of viral infection or bacterial infection which are not adequately controlled by anti-infective agents. Secondary infections are common during corticosteroid therapy. Corticosteroids may reactivate tuberculosis, and should not be used in patients with a history of active tuberculosis except when chemoprophyl axis is instituted concomitantly. Patients receiving immunosuppressive doses of corticosteroids should be advised to avoid exposure to *measles* or *varicella*, and if exposed to these diseases, to seek medical advice immediately. In general, corticosteroids should not be used in patients with herpes infection.

Patients should be instructed to notify their physician immediately if signs of infection or injury occur, both during treatment, or up to 12 months following cessation of therapy. Dosages should be adjusted, or glucocorticoid therapy reintroduced, if required. If surgery is required, patients should advise the attending physician of the corticosteroid they have received within the last 12 months, and the disease for which they were being treated. Identification cards which include the name of the patient's disease, the currently administer ed type and dose of corticosteroid, and the patient's physician should be carried with the patient at all times.

Corticosteroid therapy has been associated with left ventricular free-wall rupture in patients with recent myocardial infarction, and should therefore be used cautiously in these patients.

Corticosteroids cause edema, which may exacerbate congestive heart failure or hypertension, and should be used with caution in these patients.

Corticosteroids should be used cautiously in patients with glaucoma or other visual disturbance. Corticosteroids are well known to cause cataracts and can exacerbate glaucoma during long-term administration. Patients receiving topical or systemic corticosteroids chronically should be periodically assessed for cataract formation.

Corticosteroids should be used with caution in patients with GI disease, diverticulitis, intestinal anastomosis (because of the possibility of perforation), or hepatic disease causing hypoalbuminemia such as cirrhosis. While used for the short-term treatment of acute exacerbations of chronic inflammatory bowel disease such as ulcerative colitis and Crohn's disease, corticosteroids should not be used in patients where there is a possibility of impending GI perforation, abscess, or pyogenic infection. Some patients may require long-term corticosteroid therapy to suppress disease activity, but generally this practice is not recommended. Corticosteroids

should not be used in patients with peptic ulcer disease except under life-threatening circumstances.

Corticosteroids should be used with extreme caution in patients with psychosis, emotional instability, herpes simplex ocular infections, renal disease, osteoporosis, diabetes mellitus, and seizure disorder, because the drugs may exacerbate these conditions. Patients with hypothyroidism may have an exaggerated response to corticosteroids, thus any steroid should be used with caution in these patients.

Glucocorticoids should be used with caution in patients with myasthenia gravis who are being treated with anticholinesterase agents (see Interactions). Muscle weakness may be transiently increased during the initiation of glucocorticoid therapy in patients with myasthenia gravis, necessitating respiratory support.

Glucocorticoids may rarely increase blood coagulability and cause intravascular thrombosis, thrombophlebitis, and thromboembolism. Therefore, corticosteroids should be used with caution in patients with coagulopathy or thromboembolic disease.

Increased dosages of rapid-acting corticosteroids may be necessary for patients undergoing physiologic stress, such as major surgery, acute infection, or blood loss. The corticosteroid should be administered before, during, and after the stressful situation.

Complications including cleft palate, still birth, and premature abortion have been reported when corticosteroids were administered during pregnancy. If these drugs must be used during pregnancy, the potential risks should be discussed with the patient. Babies born to women receiving large doses of corticosteroids during pregnancy should be monitored for signs of adrenal insufficiency and appropriate therapy initiated, if necessary. Prednisone is classified as category B but cortisone is classified as pregnancy category D. This probably reflects the fact that cortisone is more commonly used during pregnancy than is prednisone and therefore, more reports of problems have been associated with cortisone than prednisone and not the fact that it is a more potent teratogen. Corticosteroids distribute into breast milk, and the manufacturer states that women receiving pharmacological dosages of corticosteroids should not practice breast-feeding.

Corticosteroid therapy usually does not contraindicate vaccination with live-virus vaccines when such therapy is of short-term (< 2 weeks); low to moderate dose; long-term alternate day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy); or via topical administration (skin or eye), by aerosol, or by intra-articular, bursal or tendon injection. The immunosuppressive effects of steroid treatment differ, but many clinicians consider a dose equivalent to either 2 mg/kg/day or 20 mg/day of prednisone as sufficiently immunosuppressive to raise concern about the safety of immunization with live-virus vaccines. In general, patients with severe immunosuppression due to large doses of corticosteroids should not receive vaccination with live-virus vaccines. When cancer chemotherapy or immunosuppressive therapy is being considered (e.g., for patients with Hodgkin's disease or organ transplantation), vaccination should precede the initiation of chemotherapy or immunotherapy by >2 weeks. Patients vaccinated while on immunosuppressive therapy or in the 2 weeks prior to starting therapy should be considered unimmunized and should be revaccinated at least 3 months after discontinuation of therapy. In patients who have received high-dose, systemic corticosteroids for >2 weeks, it is recommended to wait at least 3 months after discontinuation of therapy before administering a live-virus vaccine.

Prolonged therapy with corticosteroids should be avoided in children, as the drug may retard bone growth. Children receiving corticosteroids are immunosuppressed, and are therefore more susceptible to infection. Normally innocuous infections can become fatal in these children, and care should be taken to avoid exposure to these diseases.

As glucocorticoids can produce or aggravate *Cushing's syndrome,* glucocorticoids should be avoided in patients with Cushing's disease.

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression. Acute adrenal insufficiency and even death may occur following *abrupt discontinuation*. Withdrawal from prolonged oral corticosteroid therapy should be gradual; HPA suppression can last for up to 12 months following cessation of therapy, and patients may need supplemental corticosteroid treatment during periods of physiologic stress, such as surgery, acute blood loss, or infection, even after the drug has been discontinued. Also, a non-HPA withdrawal syndrome may occur following abrupt discontinuation of corticosteroid therapy, and is apparently unrelated to adrenocortical insufficiency. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see Adverse Reactions).

Drug Interactions

- Amphotericin B
- Anticoagulants
- Antidiabetic Agents
- Antithyroid agents
- Barbiturates
- Cholinesterase Inhibitors
- Digoxin
- Diuretics
- Dofetilide
- Estrogens
- Isoproterenol
- Mifepristone, RU-486
- Neuromuscular blockers
- Nevirapine
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Phenytoin
- Porfimer
- Rifabutin
- Rifampin
- Ritonavir
- Salicylates
- Thyroid hormones
- Toxoids
- Vaccines

Hepatic microsomal enzyme inducers including barbiturates, phenytoin, rifabutin and rifampin may increase the metabolism of glucocorticoids. Rifabutin and rifampin are particularly potent enzyme inducers. Despite the fact that prednisone is converted in the liver to its active form, prednisolone, prednisolone is also metabolized by the liver and susceptible to accelerated clearance if any of these drugs are added. Dosages of prednisone may require adjustment if these agents, especially rifabutin or rifampin, are initiated or withdrawn during therapy.

Estrogens may increase the concentration of transcortin, thus reducing the amount of unbound cortisone. In addition, estrogens have been shown to decrease the clearance of prednisolone. Since prednisone is metabolized to prednisolone, this interaction should also apply to prednisone. Therefore, the effects of corticosteroids may be altered by the concurrent administration of estrogen, requiring the adjustment of corticosteroid dosages if estrogen is added to or withdrawn during therapy.

The risk of GI ulceration from nonsteroidal anti-inflammatory drugs (NSAIDs) may be increased with corticosteroid therapy. Aspirin, ASA should be used with caution in patients with hypoprothrombinemia who are also receiving corticosteroids. Serum salicylate levels may increase when corticosteroid therapy is discontinued, possibly due to a decrease in corticosteroid-induced metabolism of salicylates. This may rarely precipitate salicylate toxicity. Patients receiving these drugs concomitantly should be observed closely for evidence of adverse effects.

The potassium-wasting effects of corticosteroid therapy may be exacerbated by concomitant administration of other potassium depleting drugs including thiazide diuretics, furosemide, ethacrynic acid and amphotericin B. Serum potassium levels should be monitored in patients receiving these drugs concomitantly.

Glucocorticoids interact with cholinesterase inhibitors, including ambenonium, neostigmine and pyridostigmine, causing severe muscle weakness in patients with myasthenia gravis who receive these drugs concomitantly. Glucocorticoids are used therapeutically, however, in the treatment of some patients with myasthenia gravis.

Killed or inactivated vaccines and toxoids do not represent a danger to immunocompromised persons and generally should be administered as recommended for healthy persons. The immune response of immunocom promised persons to vaccines is not as good as healthy persons; higher doses or more frequent boosters may be required, although the immune response still may be suboptimal. Live-virus vaccines should not be given to immunocompromised individuals due to the potentiation of virus replication and adverse reactions to the virus. Those undergoing high-dose corticosteroid therapy should not be exposed to others who have recently received the oral poliovirus vaccine (OPV). Measles-mumps-rubella (MMR) vaccination is not contraindicated for the close contacts, including health care professionals, of immunocompromised patients. Passive immunoprophylaxis with immune globulins may be indicated for immunocompromised persons instead of, or in addition to, vaccination. When exposed to a vaccine-preventable disease such as measles, severely immunocompromised children should be considered susceptible regardless of their vaccination history.

Corticosteroid therapy may rarely increase blood coagulability. Patients receiving heparin or warfarin may experience loss of clinical effect. In addition, corticosteroids have been associated with gastrointestinal bleeding. Thus, corticosteroids should be used cautiously in patients receiving anticoagulants.

The metabolism of corticosteroids is increased in hyperthyroidism and decreased in hypothyroidism. Dosage adjustments may be necessary when initiating, changing or discontinuing thyroid hormones or antithyroid agents.

Systemic corticosteroids increase blood glucose levels; a potential pharmacodynamic interaction exists between corticosteroids and all antidiabetic agents. Diabetic patients who are administered systemic corticosteroid therapy may require an adjustment in the dosing of the antidiabetic agent. Blood lactate concentrations and the lactate to pyruvate ratio increased when metformin was coadministered with corticosteroids (e.g., hydrocortisone). Elevated lactic acid concentrations are associated with an increased risk of lactic acidosis, so patients on metformin concurrently with systemic steroids should be monitored closely.

Patients receiving digoxin and corticosteroids concomitantly are at an increased risk for developing arrhythmias or digitalis toxicity due to corticosteroid-induced hypokalemia. Corticosteroid-induced hypokalemia could also enhance the proarrhythmic effects of dofetilide. Hypokalemia also potentiates neuromuscular blockade associated with nondepolarizing neuromuscular blockers. Corticosteroids should be monitored closely when used with neuromuscular blockers.

Corticosteriods administered prior to or concomitantly with porfimer photodynamic therapy may decrease the efficacy of the treatment.

The risk of cardiac toxicity with isoproterenol in asthma patients appears to be increased with the coadministration of corticosteroids or methylxanthines. Intravenous infusions of isoproterenol in refractory asthmatic children at rates of 0.05-2.7 ug/kg/min have caused clinical deterioration, myocardial infarction (necrosis), congestive heart failure and death.

Mifepristone, RU-486 exhibits antiglucocorticoid activity that may antagonize the corticosteroids. In rats, the activity of dexamethasone was inhibited by oral mifepristone doses of 10—25 mg/kg. A mifepristone dose of 4.5 mg/kg in humans resulted in compensatory increases in ACTH and cortisol. Mifepristone is contraindicated in patients on long-term corticosteroid therapy.

Due to ritonavir inhibition of hepatic enzymes, drug-drug interactions may occur during concurrent administration with prednisone.

In a clinical trial, concomitant use of prednisone (40 mg/day for the first 14 days of nevirapine administration) was associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, the use of prednisone to prevent nevirapine-associated rash is not recommended.

Adverse Reactions

- abdominal pain
- acne vulgaris
- adrenocortical insufficiency
- amenorrhea
- angioedema
- anorexia
- anxiety
- appetite stimulation
- arthralgia
- avascular necrosis
- bone fractures
- cataracts
- constipation
- Cushing's syndrome
- depression
- diabetes mellitus
- diaphoresis
- diarrhea
- dysmenorrhea
- ecchymosis
- edema
- EEG changes
- emotional lability
- erythema
- esophageal ulceration
- euphoria
- exfoliative dermatitis
- exophthalmos
- fever
- fluid retention
- impaired wound healing
- increased intracranial pressure
- infection
- insomnia
- lethargy
- menstrual irregularity
- metabolic alkalosis
- mood lability
- myalgia
- myopathy
- nausea/vomiting
- ocular hypertension
- optic neuritis
- osteoporosis
- palpitations
- pancreatitis
- papilledema
- peptic ulcer
- peripheral neuropathy
- petechiae
- phlebitis
- physiological dependence
- pseudotumor cerebri
- psychosis
- restlessness
- retinopathy
- seizures
- sinus tachycardia
- skin atrophy
- sodium retention

- gastritis
- growth inhibition
- headache
- heart failure
- hirsutism
- hypercholesterolemia
- hyperglycemia
- hypernatremia
- hypertension
- hypocalcemia
- hypokalemia
- hypotension
- hypothalamic-pituitary-adrenal (HPA) suppression
- immunosuppression
- striae
- thrombocytopenia
- thromboembolism
- thrombosis
- urinary incontinence
- urinary urgency
- urticaria
- vertigo
- visual impairment
- weakness
- weight gain
- weight loss
- withdrawal

NOTE: Prolonged administration of *physiologic* replacement dosages of glucocorticoids does not usually cause adverse effects. The severity of the adverse effects associated with prolonged administration of *pharmacological* dosages of corticosteroids increases with duration of therapy. Short term administration of large doses typically does not cause adverse effects, but long term administration can lead to adrenocortical atrophy and generalized protein depletion.

Glucocorticoids are responsible for protein metabolism, and prolonged therapy can result in various musculoskeletal manifestations, including: myopathy (myalgia, muscle wasting, muscle weakness), impaired wound healing, bone matrix atrophy (osteoporosis), bone fractures such as vertebral compression fractures or fractures of long bones, and avascular necrosis of femoral or humoral heads. These effects are more likely to occur in older or debilitated patients. Glucocorticoids interact with calcium metabolism at many sites, including: decreasing the synthesis by osteoblasts of the principle proteins of bone matrix, malabsorption of calcium in both the nephron and the gut, and reduction of sex hormone concentrations. Although all of these actions probably contribute to glucocorticoid-induced osteoporosis, the actions on osteoblasts is most important. Glucocorticoids do not modify vitamin D metabolism.[1441] Postmenopausal women, in particular, should be monitored for signs of osteoporosis during corticosteroid therapy. Because of retardation of bone growth, children receiving prolonged corticosteroid therapy may have growth inhibition.

Corticosteroid therapy can mask the symptoms of infection and should be avoided during an acute viral or bacterial infection. Immunosuppression is most likely to occur in patients receiving high-dose (e.g., equivalent to 1 mg/kg or more of prednisone daily), systemic corticosteroid therapy for any period of time, particularly in conjunction with corticosteroid sparing drugs (e.g., troleandomycin) and/or concomitant immunosuppressant agents; however, patients receiving moderate dosages of systemic corticosteroids for short periods or low dosages for prolonged periods also may be at risk. Corticosteroids can reactivate tuberculosis and should not be used in patients with a history of active tuberculosis except when chemoprophylaxis is instituted concomitantly. Patients receiving immunosuppressive doses of corticosteroids should be advised to avoid exposure to measles or varicella (chickenpox) and, if exposed to these diseases, to seek medical advice immediately.

Corticosteroids are divided into two classes: mineralocorticoids and glucocorticoids. Mineralocorticoids alter electrolyte and fluid balance by facilitating sodium retention and hydrogen and potassium excretion at the level of the distal renal tubule, resulting in edema and hypertension. Mineralocorticoid properties can cause fluid retention; electrolyte disturbances (hypokalemia, hypokalemic metabolic alkalosis, hypernatremia, hypocalcemia), edema, and hypertension. Prolonged administration of glucocorticoids may also result in edema and hypertension. In a review of 93 studies of corticosteroid use, hypertension was found to develop 4 times as often in steroid recipients compared to control groups.[938] Congestive heart failure may also occur in susceptible patients.

Although corticosteroids are used to treat Graves' ophthalmopathy, ocular effects, such as exophthalmos, posterior subcapsular cataracts, retinopathy, or ocular hypertension, can result from prolonged use of glucocorticoids and could result in glaucoma or ocular nerve damage including optic neuritis. Temporary or permanent visual impairment, including blindness, has been reported with glucocorticoid administration by several routes of administration including intranasal and ophthalmic administration. Secondary fungal and viral infections of the eye can be exacerbated by corticosteroid therapy.

Prolonged corticosteroid therapy may adversely affect the endocrine system, resulting in hypercorticism (Cushing's syndrome), menstrual irregularity including dysmenorrhea or amenorrhea, hyperglycemia, and aggravation of diabetes mellitus in susceptible patients. In a recently-published review of 93 studies of corticosteroid use, the development of diabetes mellitus was determined to occur 4 times more frequently in steroid recipients compared to control groups.[938] In patients with preexisting diabetes mellitus, insulin or oral hypoglycemic dosages may require adjustment during steroid administration.

Adverse GI effects associated with corticosteroid administration include nausea/vomiting and anorexia with subsequent weight loss. Appetite stimulation with weight gain, diarrhea, constipation, abdominal pain, esophageal ulceration, gastritis, and pancreatitis have also been reported. Although it was once believed that corticosteroids contributed to the development of peptic ulcer disease, in a published review of 93 studies of corticosteroid use, the incidence of peptic ulcer disease was not found to be higher in steroid recipients compared to control groups.[938] While most of these studies did not utilize endoscopy, it is unlikely that corticosteroids contribute to the development of peptic ulcer disease.

Adverse neurologic effects have been reported during prolonged corticosteroid administration and include headache, insomnia, vertigo, restlessness, ischemic peripheral neuropathy, seizures, and EEG changes. Mental disturbances, including mood lability, depression, anxiety, euphoria, personality changes, and psychosis, have also been reported; emotional lability and psychotic problems can be exacerbated by corticosteroid therapy.

Various adverse dermatologic effects reported during corticosteroid therapy include skin atrophy, acne vulgaris, diaphoresis, impaired wound healing, facial erythema, striae, petechiae, hirsutism, ecchymosis, and easy bruising. Hypersensitivity reactions may manifest as allergic dermatitis, urticaria, and/or angioedema.

Pharmacologic doses of corticosteroids administered for prolonged periods may result in physiological dependence due to hypothalamic-pituitary-adrenal (HPA) suppression. Exogenous corticosteroids exert negative feedback on the pituitary, inhibiting the secretion of adrenocorticotropin (ACTH). This results in a decrease in ACTH-mediated synthesis of endogenous corticosteroids and androgens by the adrenal cortex. The severity of glucocorticoid-induced secondary adrenocortical insufficiency varies among individuals, and is dependent upon the dose, frequency, time of administration, and duration of therapy. Administering the drug on alternate days may help to alleviate this adverse effect. Patients with HPA suppression will require increased doses of corticosteroid therapy during periods of physiologic stress. Acute adrenal insufficiency and even death may occur if sudden withdrawal of the drugs is undertaken. Withdrawal from prolonged oral corticosteroid therapy should be gradual; HPA suppression can last for up to 12 months following cessation of therapy, and patients may need supplemental corticosteroid treatment during periods of physiologic stress, such as surgery, acute blood loss, or infection, even after the drug has been discontinued. Also, a non-HAP withdrawal syndrome may occur following abrupt discontinuance of corticosteroid therapy, and is apparently unrelated to adrenocortical insufficiency. This syndrome includes symptoms such as anorexia, lethargy, nausea/vomiting, headache, fever, arthralgia, myalgia, exfoliative dermatitis, weight loss, and hypotension. These effects are thought to be due to the sudden change in

glucocorticoid concentration rather than to low corticosteroid levels. Increased intracranial pressure with papilledema (i.e., pseudotumor cerebri) has also been reported with withdrawal of glucocorticoid therapy.

Hypercholesterolemia, atherosclerosis, fat embolism, thrombosis, thromboembolism, and phlebitis, specifically, thrombophlebitis have been associated with corticosteroid therapy. Thrombocytopenia has occurred in several patients receiving prolonged, high-dose corticosteroid therapy. Palpitations, sinus tachycardia, glossitis, stomatitis, urinary incontinence, and urinary urgency have been rarely reported. Corticosteroids may also decrease serum concentrations of vitamin C (ascorbic acid) and vitamin A which may rarely produce symptoms of vitamin A deficiency or vitamin C deficiency.

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APPENDIX 3: CICLOSPORIN DRUG INFORMATION SHEET

http://www.panacea-biotec.com/profile.htm
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Panimun Bioral
Cyclosporine USP

Panimun Bioral Solution
(Cyclosporine Oral Solution USP-100 mg/ml)

Description
Pale yellow coloured, clear liquid.

Composition
Each ml of solution contains:
Cyclosporine USP.....100 mg.

Panimun Bioral 25 mg
(Cyclosporine Capsules USP-25 mg)

Description
Reddish brown coloured, oval shaped, soft gelatin capsules containing pale yellow coloured, clear liquid.

Composition
Each soft gelatin capsule contains:
cyclosporine USP..... 25 mg
Approved colours used in capsule shells

Panimun Bioral 50 mg
(Cyclosporine Capsules USP-50 mg)

Description
Coffee browm coloured, oblong shaped, soft gelatin capsules containing pale yellow coloured, cleared liquid.

Composition
Each soft gelatin capsule contains:
cyclosporine USP..... 50 mg
Approved colours used in capsule shells

Panimun Bioral 100 mg
(Cyclosporine Capsules USP-100 mg)

Description
Reddish brown coloured, oblong shaped, soft gelatin capsules containing pale yellow coloured, clear liquid.

Composition
Each soft gelatin capsule contains:
cyclosporine USP..... 100 mg
Approved colours used in capsule shells

PROPERTIES
The cyclosporine (also known as cyclosporine A) is a lipophillic cyclic polypeptide composed of 11 amino acids[1]. It is a potential immunosuppressor which has shown to be able to prolong in animals, the survival of transplants such as skin, heart, kidneys, pancreas, bone marrow, small intestine and lungs.
Various studies on animals have proved that cyclosporine inhibits the development of cell mediated immunity including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, reaction from transplantation towards host (graft versus host disease, GVHD) and the production of T cell

dependent antibodies. Cyclosporine inhibits the production as well as the release of lymphokines such as interleukin 2[2](T cell growth factor, TCGF). From experimental data it can be noticed that cyclosporine blocks the quiescent lymphocytes in phase G or at the beginning of phase G_1 of the cellular cycle.
All the available data indicates that cyclosporine acts on the lymphocytes in a specific and reversible manner. Cyclosporine does not depress hemopoiesis and does not alter the function of phagocytes. Patients treated with cyclosporine are less susceptible to infections as compared to those that receive another immunosuppressive treatment.
In human beings cyclosporine has given positive results in kidney transplants, bone marrow transplants to prevent and treat rejection and GVHD, and in a series of diseases of autoimmune origin.

PHARMACOKINETICS
After oral administration (oral solution and capsules) the peak plasma blood concentration is reached between the first and third hour. Absolute bio-availability of oral preparation in stationery state is 20-50% (average 34%).
The C_{max}, T_{max} and $AUC_{0\text{-}24hrs}$ of Panimun Bioral solution was 858.06 $\pm$ 54.22 ng/ml, 1.42 $\pm$ 0.11 hrs and 2995.78 $\pm$ 139.32 ng hr ml^{-1} respectively, after a single dose of 1.8 ml solution equivalent to 180 mg cyclosporine[3]. The C_{max}, T_{max} and $AUC_{0\text{-}12hrs}$ of Panimun Bioral Capsule was 792.94 $\pm$ 54.07 ng/ml, 2.09 $\pm$ 0.08 hrs and 3266.71 $\pm$ 197.12 ng hr ml^{-1} respectively, after single oral dose of 175 mg capsule.[4] Assay employed was Radio Immuno Assay. The mean elimination half life (t½) of single oral dose of solution and capsule was 4.87 $\pm$ 1.73 hrs and 4.80 $\pm$ 1.58 hrs respectively.
Cyclosporine is distributed in large part outside the blood volume. In blood, distribution is saturation dependent. Approximately 33-47% is found in the plasma, 4-9% in lymphocytes, 5-12% in granulocytes, 41-58% in erythrocytes. In plasma approximately 90% is bound to proteins primarily lipoproteins. Disposition of cyclosporine from blood is biphasic. Elimination is mainly biliary and only 6% of dose is excreted in urine. Cyclosporine is extensively metabolised with no major metabolic pathway. Only 0.1% of unchanged drug is excreted in urine.

THERAPEUTIC INDICATIONS
a) *Organ transplantation*
Cyclosporine is indicated as immunosuppressor for the prevention of refusal (or rejection) of allogenic transplantation of kidney, liver, heart, lung and pancreas. It may be used alone or in association with other immunosuppressants with low doses of corticosteroids.
Cyclosporine may also be used in the treatment for rejection of transplantation in patients who have received previously other immunosuppressants.
b) *Bone-marrow transplantation & Aplastic Anaemia*
Cyclosporine is indicated as immunosuppressor in the prevention of rejection of bone marrow transplantation and or in the prevention and in the therapy of the graft versus host disease (GVHD) alone or in combination with other drugs.
c) *Endogenous uveitis*
Cyclosporine is indicated for treatment of posterior or intermediate uveitis of non infectious origin in active phase, with grave risk of loss of visual function, when the other conventional therapies have not proven to be effective or when they provoke unacceptable side effects.
Cyclosporine is also indicated for treatment of uveitis in the Behcet's Syndrome, with repeated inflammatory attacks of the retina.
d) *Psoriasis*
Cyclosporine is indicated for patients with serious psoriasis, in whom the conventional therapies have proved to be ineffective or inappropriate.
e) *Rheumatoid arthritis*
Cyclosporine is indicated for the treatment of severe rheumatoid arthritis in active phase, in whom the classic antirheumatic medicines are inefficient and inappropriate.
f) *Nephrotic syndrome*
Cyclosporine can be used to induce remissions and to maintain the patients of steroid-dependent and steroid resistant nephrotic syndrome due to glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis or membranous glomerulonephritis.
g) *Unlabelled indications*

Other conditions where cyclosporine can be used are primary biliary cirrhosis, atopic dermatitis, lichen planus, pyoderma gangrenosum, alopecia areata, bullous disorders, psoriasis vulgaris, ulcerative colitis, crohn's disease, chronic viral active hepatitis, auto immune chronic active hepatitis, nephrotic syndrome, type I (Insulin dependent) diabetes mellitus and to a limited extent in myasthenia gravis and multiple sclerosis.

CONTRAINDICATIONS
Hypersensitivity is known for cyclosporine.

PRECAUTIONS
Cyclosporine must be used only by medical specialists who have experience of immunosuppressive therapy and/or of treatment of organ transplantation or transplantation of bone marrow. Patients receiving cyclosporine must be followed by centres equipped with appropriate laboratory facilities and adequate support of medical personnel.
Patients with malabsorption syndrome may have difficulty in achieving therapeutic levels.
Hypertension is a common side effect of cyclosporine therapy. Generally mild to moderate hypertension is seen. However, on continuous administration incidence decreases with time. Antihypertensives are generally recommended for this. Since hyperkalaemia may be seen with cyclosporine therapy, potassium sparing diuretics are not recommended for treating this condition. In such patients calcium antagonists can be effective agents for treating such hypertension. Due to alterations in metabolism of cyclosporine by some calcium antagonists, dosage adjustments of cyclosporine may be required.
During treatment with cyclosporine, vaccination may be less effective. Use of live attenuated vaccines should be avoided
Repeated laboratory tests for renal, liver functions should be done to know the status of kidney and liver. Since cyclosporine has tendency to alter lipid profile, it is advisable to evaluate the lipid profile before and after treatment and after first month of therapy. In case of significant increase, it is advisable to restrict dietary fats and if necessary reduce cyclosporine dosage.
Use cautiously in the treatment of patients with hyperuricemia. The dosage must be inspected rigorously. Laboratory checks should be done periodically.
In case of infections, even trivial ones (cold, influenza etc.) the doctor must be immediately informed.
For monitoring of the serum level of cyclosporine in whole blood, use of methods based on specific monoclonal antibodies (RIA methods) or by HPLC are preferred. A standard separation protocol (time and temperature) should be followed. It is necessary to keep in mind that the concentration of cyclosporine in the blood, is only one of the many factors that contribute to the clinical state of the patient. The repeated serum levels must therefore, be utilised as a guideline for determining the dosage in the context of the other clinical or laboratory parameters.

SPECIAL WARNINGS
Cyclospoprine has not been shown to be teratogenic in animals. Experience with cyclosporine in pregnant females is still limited. Data relative to women subjected to organ transplantation indicate that, in comparison with the traditional immunosuppressive therapy, cyclosporine does not provoke any additional risk on the course and outcome of pregnancy. However, there are no adequate well controlled studies in pregnancy and hence cyclosporine should be used during pregnancy only if potential benefits outweigh the risk to foetus.
Safety during lactation:
Infants of women receiving cyclosporine should not be breast-fed as the drug passes into breast milk.

Cyclosporine in children:
Experience with cyclosporine in children is still limited. However, children of the age of 1 year and above have received cyclosporine in standard dose with no particular problems. In many studies pediatric patients have required and tolerated higher doses of cyclosporine per kg of body weight, in comparison with those used in adults.

INTERACTIONS

Particular attention must be paid in administering cyclosporine in association with medicines with noted nephrotoxic effects, for example aminoglycosides, amphotericin B, ciprofloxacin, digoxin, melfalan, colchicine and trimethoprim.
Since nonsteroidal antiinflammatory drugs (NSAIDs) may alter the renal function, association of these with cyclosporine or an increase of their dosage, must be accompanied in the initial phase by an attentive monitoring of the renal function.
Cyclosporine can increase the risk of muscular toxicity, including pain and weakness of muscles which may be noticed in the course of treatment with lovastatine. Hence, use of such medicines along with cyclosporine must be attentively and carefully considered. It is known that various medicines are capable of increasing or decreasing serum concentration of cyclosporine acting through competitive inhibition or induction of hepatic enzymes (in particular cytochrome P450) involved in the metabolism and excretion of cyclosporine. The following medicines can increase the serum levels of cyclosporine, e.g. ketoconazole, some macrolide antibiotics including erythromycin and josamycine, methyl prednisolone, metoclopramide, ranitidine, amiodarone, itraconazole, danazol, metronidazole, norfloxacin, and some calcium channel antagonists such as diltiazem, nicardipine and verapamil. Avoid taking nifedipine for patients who have developed gingival hypertrophy. Among the medicines that decrease the concentration of cyclosporine in plasma or in the whole blood, following have been indicated; barbiturates, carbamazepine, phenytoin and rifampicin. Hence, it is recommended that administration of cyclosporine along with these medicines must be avoided. If the concomitant administration of cyclosporine and one of these medicines is inevitable, blood concentration of cyclosporine must be monitored and appropriate modifications of dosage of cyclosporine must be brought about.

SIDE EFFECTS
The side effects are dose dependent and regress with the reduction of the dose. Those observed more frequently include hypertrichosis, tremors, renal dysfunction, hypertension, hepatic dysfunction, fatigue, gingival hypertrophy, gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea) and sensation of burning of the hands and feet (usually during - the first week of the treatment). Occasionally headache and rashes, possibly of allergic origin are observed, besides slight anaemia, hyperkalemia, hyperuricemia, hypomagnesemia, increase in weight, oedema, pancreatitis, paresthesia and convulsions. In rare cases muscular cramps, muscular weakness and myopathy have been observed. Especially in patients who have undergone liver transplantation, signs of encephalopathy, disturbances of vision and movement and altered consciousness have been observed. It has not yet been established if such alterations are caused by cyclosporine, by the underlying pathology itself, or by other conditions. Rarely a syndrome of thrombocytopenia and microangiopathic hemolytic anaemia and renal failure (hemolytic uremic syndrome) has been observed. In some patients neoplasms or lymphoproliferative disorders have been observed but their incidence and distribution is similar to those in patients who have undergone conventional immunosuppressive therapy.

POSOLOGY AND FREQUENCY OF ADMINISTRATION
The intervals of dosage specified successively must be understood as per indications and references. Regular monitoring of the cyclosporine blood levels is advised.
a) Solid Organ Transplantation
The initial dose of cyclosporine equal to 10-15 mg/kg of cyclosporine[5] must be administered within 12 hours before the operation in one intake. As a general rule, the same daily dose must be administered even after the operation for one or two weeks; then reduce the daily dose by five percent per week in accordance with the blood levels, till a maintenance dose of 2-6 mg/kg/day in divided doses. Cyclosporine concentrate for intravenous infusion can be used in case of gastroenteric intolerance so as to compromise the absorption of the oral preparations of the medicine. It is advised to change to oral preparations as soon as possible.
If cyclosporine is utilised in association with other immunosuppressive medicines (e.g. with corticosteroids or when triple or quadruple immunosuppressive therapy is necessary), lesser doses may be used (e.g. 3 to 6 mg/Kg/day given in two divided doses for initial treatment).
b) *Bone Marrow Transplantation*
The initial dose of cyclosporine must be administered the day preceeding that of transplantation. In majority of the cases one prefers to use the concentrate for intravenous

infusion at a dose of 2.5-5 mg/kg/day as initial dose and in the period following immediately the transplantation for a duration of not more than 2 weeks to pass on to the maintenance therapy by oral method at a dose of 12.5 mg/kg/day.[6]
In case of gastrointestinal complications that may reduce the absorption of medicine, a higher oral or intravenous dosage may be necessary. Cyclosporine may be given to initiate the treatment. In this case the advised dose is of 12.5-15 mg/kg/day in two divided doses from the first day of transplantation.
The maintenance therapy must be prolonged for at least 3-6 months (preferably 6 months) before reducing gradually to zero after one year.
In some patients, discontinuation of cyclosporine may result in GVHD. In this case generally a positive response is obtained with the resumption of administration of cyclosporine. Low dose cyclosporine should be used to treat mild chronic GVHD. Intravenous cyclosporine is advised to be used in the treatment at a dose of 3.5 mg/kg/day, till the time the medicine cannot be taken orally. If possible oral administration at a dose of 12.5-15 mg/kg/day may be utilised right from the beginning. Initial posology must be maintained for about 2 months, reducing then gradually the dose (5% every week) till reaching 2 mg/kg/day. At such dosage the treatment can be suspended.

c) Aplastic Anaemia

The exact cyclosporine dosage has not yet been formalised in patients of aplastic anaemia However, cyclosporine in initial dosage should be given in range of 3 to 7 mg/kg/day[2] adjusted according to the response and serum creatinine levels. Cyclosporine should be continued for at least 3 months and until peripheral blood count has stabilized for at least one month and then drug is tapered off slowly.

d) *Endogenous Uveitis (including Behcet's syndrome)*

It is recommended to start with an oral dose of 5 mg/kg/day in two divided doses[2] till remission of the active inflammation of the uvea and improvement of vision is achieved. In refractory cases, dose can be increased to 7 mg/kg/day for a limited period, on condition that cyclosporine is tolerated and that alterations of biochemical parameters (creatininemia) or of blood pressure are not present.
For obtaining the initial remission or for controlling repeated inflammatory ocular attacks, cyclosporine is administered in concomitance with systemic corticosteroids if cyclosporine alone provides insufficient control (0.2-0.6 mg/kg/day equivalent to prednisone or equivalent doses of other corticosteroids).
In the maintenance therapy, the posology must be decreased gradually to the minimum effective dose so that during the phase of remission it should not surpass 5 mg/kg/day.

Warning

Since cyclosporine may alter the renal function, only patients with normal renal function must be treated. It is necessary to frequently evaluate the renal function and reduce the dose by 25-50% if the serum creatinine increases beyond 30% of the value recorded before starting the therapy even if such value is in the normal range. If an improvement of the intraocular inflammation is not obtained after 3 months of treatment with cyclosporine at adequate doses and in association with steroids, the possibility of adopting alternative therapies must be looked into.

e) *Psoriasis*

For inducing remission, it is recommended to start with 2.5 mg/kg/day orally in two divided[2] doses. If no improvement is noted within a month gradually increase the posology without surpassing 5mg/kg/day. In patients who do not show adequate response after 6 months of the therapy at a dose of 5 mg/kg/day, it is better to discontinue the administration; it is also better to discontinue it in patients in whom the minimum effective dose is not compatible with the norms given later (see warnings) for ensuring the treatment. It is possible to begin the therapy with 5 mg/kg/day in patients in whom rapid improvement is required due to seriousness of the disease.
For every patient the minimum effective dose of maintenance must be established, such dose should not exceed 5 mg/kg/day.

Warning

Patients with altered renal function, uncontrolled hypertension, clinically relevant infections or any type of malignancy (excluding the cutaneous ones, see later), should not be treated with cyclosporine. In patients with hyperuricemia or hyperkalemia, caution is necessary.
Since cyclosporine may worsen the renal function, it is advisable to measure the serum creatinine levels every two weeks for the first three months of the therapy; subsequently in

patients treated with 2.5 mg/kg/day, if serum creatinine remains stable, carry out a check every 2 months and monthly in those treated with higher doses. It is necessary to reduce the dose by 25-50% if the creatininemia increases beyond 30% with respect to base value, even if the values are in the normal range. If such reduction does not bring about the desired corrections of the parameter within one month, interrupt the treatment with cyclosporine. If in the course of the treatment an uncontrollable hypertension is set up even with an appropriate antihypertensive therapy, it is better to interrupt the treatment.
In patients with psoriasis, treated with cyclosporine or with other therapies, appearance of neoplasm, particularly of skin is reported. Cutaneous lesions, not typical of psoriasis which could make one think to be neoplastic or preneoplastic lesions, must be subjected to biopsy before initiating the treatment with cyclosporine. The patients who show cutaneous preneoplastic or neoplastic alterations can initiate the treatment with cyclosporine only after an adequate treatment of such lesions, and only if successful alternative therapy does not exist. Rarely appearance of lymphoproliferative disorders is observed in patients of psoriasis treated with cyclosporine which is readily reversible on suspension of the treatment.

f) *Rheumatoid arthritis*

The initial cyclosporine dose should range from 2.5 to 3.5 mg/kg/day[2] with a maximum dosage of 5 mg/kg/day increased at 1-2 month interval by 0.5 mg/kg/day if clinical response is not seen. In responders cyclosporine dosage should be slowly reduced by 0.5 mg/kg/day, decrements every 1-2 months to lowest effective dosage.
In the subsequent maintenance therapy the dose must be adapted for individual patients in accordance with tolerability. Cyclosporine can be administered in combination with low doses of corticosteroids and/or non steroidal anti-inflammatory drugs.

Warning

Patients with reduced renal function, with uncontrollable hypertension or with malignant neoplasms of any type must not take cyclosporine. Since cyclosporine can alter renal function, it is necessary to determine the pretreatment value of serum creatinine carefully through at least two determinations. During the first three months of the therapy, it is advisable to monitor the levels of serum creatinine at intervals of two weeks, subsequently the determinations may be made every 4 week but a more frequent monitoring is necessary in case where the dose of cyclosporine is increased or concomitant treatment with a non steroidal anti-inflammatory drug is started. If serum creatinine reaches values exceeding 30% with respect to the base value in more than one measurement, it is necessary to reduce the dosage of cyclosporine. If the reduction of the dosage is not sufficient to decrease the values within a month, it is necessary to interrupt the treatment with cyclosporine. Interruption of the therapy may also be necessary if during the course of the treatment, uncontrollable hypertension even with appropriate antihypertensive therapy has developed. As with other immunosuppressive medicines one must keep in mind the possibility of increase of the risk of occurrence of the lymphoproliferative disorders.

g) *Nephrotic syndrome*[2]

For inducing remission, the recommended daily dose given in two divided oral doses is 5 mg/kg for adults and 6 mg/kg for children, if, except for proteinuria, renal function is normal. In patients with impaired renal function the initial dose should not exceed 2.5 mg/kg a day. The combination of cyclosporine with low doses of oral corticosteroids is recommended if the effect of cyclosporine alone is not satisfactory, especially in steroid resistant patients. If no improvement has been observed after 3 months treatment, cyclosporine therapy should be discontinued. The doses need to be adjusted individually according to efficacy (proteinuria) and safety (primarily serum creatinine) but should not exceed 5 mg/kg a day in adults and 6 mg/kg a day in children. For maintenance treatment the dose should be slowly reduced to the lowest effective level.

Warning

Since cyclosporine can impair renal function it is necessary to assess renal function frequently. If serum creatinine remains increased to more than 30% above creatinine levels recorded before starting cyclosporine therapy at more than one measurement, reduce the dosage of cyclosporine by 25 to 50%. Patients with abnormal baseline renal function should initially be treated with 2.5 mg/kg a day and must be monitored very carefully. In some patients it may be difficult to detect cyclosporine induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This explains why, in rare cases, cyclosporine associated structural kidney alterations have been observed without increases in serum creatinine. Renal biopsy should be considered for patients with steroid

dependent minimal change nephropathy in whom cyclosporine therapy has been maintained for more than one year. In patients with nephrotic syndrome treated with immunosuppressants (including cyclosporine), the occurrance of malignancies (including Hodgkin's lymphoma) has occasionally been reported.

MODE OF ADMINISTRATION

Oral Solution

For making the solution of the medicine, the syringe enclosed in the wrapping must be used.

Procedure of making oral solution :

1. Lift the plastic protection of the metallic cap
2. Remove completely the metallic cap
3. Remove the rubber plug and throw it away
4. Introduce the cannula in the bottle pushing the white cap till the mouth of the bottle.
5. Insert the syringe in the white cap of the cannula
6. Draw the required volume of solution
7. In case big air bubbles are formed inside the syringe, push the piston towards the base so that the bubbles escape from the cannula. Draw again the required volume of solution slowly. Presence of a few minute bubbles does not effect the quantity of the required dose.
8. After use, do not rinse the syringe, but clean only the external part with dry tissue paper and place it in the case. The cannula must remain in the bottle. Close the bottle with the black plastic cap provided separately.

Panimun Bioral should be diluted in a glass container (not of plastic), utilising preferably apple or orange juice (avoid grape juice). Soft drinks can be added according to individual taste. Prepare the solution immediately before taking. After having poured the medicine, mix well and drink immediately; subsequently rinse the glass with a small quantity of the same drink and drink it for ensuring that the full dose has been taken. The same drink should be continued for the entire duration of the treatment. The syringe for measuring the medicine must not get in contact with the drink. Cyclosporine solution should be used within 2 months of opening the bottle and be stored between 25 and 35^{O}C - preferably not below 25^{o}C for prolonged periods as it contains oily components of natural origin which tend to solidify at low temperatures. A jelly like formation may occur below 25^{O}C, which is however reversible at temperature up to 35^{O}C. Minor flakes or a slight sediment may still be observed. These phenomena do not affect the efficacy and safety of the product, and the dosing by means of the syringe remains accurate.

Do not utilise the solution if the aluminium seal is broken or has been removed before use.

Capsules

Panimun Bioral capsules should not be removed from the blister pack till required. On opening the blister pack one will notice a characteristic odour; it is normal and is not prejudicial to the utilisation of the medicine. The capsules must be swallowed whole and stored at temperature not exceeding 30^{O}C protected from moisture and should be administered in two divided doses.

OVERDOSAGE

Only minimal experience with overdosage is available. However, because of slow absorption of cyclosporine (capsules and solution) forced emesis would be of value up to 2 hours of administration. Transient hepatotoxicity and nephrotoxicity may occur which resolve after drug withdrawal. General supportive measures and symptomatic treatment should be followed in such cases. Cyclosporine is not dialysable to large extent and neither is cleared by charcoal hemoperfusion.

The oral LD_{50} is 2329 mg/kg in mice, 1480 mg/kg in rats and more than 1000 mg/kg in rabbits while I.V. LD_{50} is 148 mg/kg in mice, 104 mg/kg in rats and 46 mg/kg in rabbits.

CAUTION

Do not utilise the medicine after the date of expiry as indicated.

PRESENTATION

Panimun Bioral Capsules - 25 mg, 50 mg and 100 mg.
Boxes of 6 X 5's
Panimun Bioral Solution
Bottle of 50 ml

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APPENDIX 4: CICLOSPORIN IN PREGNANCY

*Pregnancy Category C: "*Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks."

Animal studies have shown reproductive toxicity in rats and rabbits. Ciclosporin gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally.) Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. Ciclosporin has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the transplant doses in humans of 6.0 mg/kg, where dose corrections are based on body surface area. Ciclosporin was embryo- and fetotoxic as indicated by increased pre- and post-natal mortality and reduced fetal weight together with related skeletal retardation.

Several case reports describe the use of Ciclosporin throughout gestation (Deeg, Kennedy et al. 1983; Lewis, Lamont et al. 1983; Flechner, Katz et al. 1985; Grischke, Kaufmann et al. 1986; al-Khader, Absy et al. 1988; Burrows, O'Neil et al. 1988; Calne, Brons et al. 1988; Kossoy, Herbert et al. 1988; Lowenstein, Vain et al. 1988; Pickrell, Sawers et al. 1988; Ziegenhagen, Crombach et al. 1988; Sims, Porter et al. 1989; Haugen, Fauchald et al. 1991; Jayaprakash, Gould et al. 2004). Most of these involved women who had received a renal transplant.

A meta-analysis looking at pregnancy outcome after cyclosporine therapy during pregnancy was published by Bar Oz (Bar Oz, Hackman et al. 2001). Ciclosporin therapy must often be continued during pregnancy to maintain maternal health in such conditions as organ transplantation and autoimmune disease. This meta-analysis was performed to determine whether Ciclosporin exposure during pregnancy is associated with an increased risk of congenital malformations, preterm delivery, or low birth weight. To assess risks of Ciclosporin exposure, a summary odds ratio was calculated. Prevalence of malformations was calculated as a rate for all Ciclosporin-exposed live births and for the subgroups identified. Fifteen studies (6 with control groups of transplant without use of cyclosporine; total patients: 410) met the inclusion criteria for major malformations, 10 for preterm delivery (4 with control groups; total patients: 379) and 5 for low birth weight (1 with control groups; total number of patients: 314). The calculated odds ratio of 3.83 for malformations did not achieve statistical significance (CI 0.75-19.6). The overall prevalence of major malformations in the study population (4.1%) also did not vary substantially from that reported in the general population. OR for prematurity [1.52 (CI 1.00-2.32)] did not reach statistical significance although the overall prevalence rate was 56.3%. The OR for low birth weight [1.5 (CI 0.95-2.44 based on 1 study)]. The analysis concludes that Ciclosporin does not appear to be a major human teratogen. It may be associated with increased rates of prematurity.

Novartis, manufacturer of Sandimune and Neoral, reports that in pregnant transplant recipients who are being treated with immuno-suppressants the risk of premature births is increased. The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred.

Most of the pregnancies (85 of 100) were complicated by disorders; including, pre-eclampsia, eclampsia, premature labour, abruptio placentae, oligohydramnios, Rh incompatibility, and fetoplacental dysfunction. Pre-term delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. Therefore, the risks and benefits of using Ciclosporin during pregnancy should be carefully weighed.

A limited number of observations in children exposed to cyclosporine *in utero* are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.(Shaheen, al-Sulaiman et al. 1993; Giudice, Dubourg et al. 2000; Tendron, Decramer et al. 2003; Cochat, Decramer et al. 2004).

Based on the relatively small numbers of cases reported, Ciclosporin during pregnancy appears not to pose a major risk to the foetus. At therapeutic doses, it is not an animal teratogen, and it is unlikely to be human teratogen. No patterns of defects have emerged in the few born with anomalies. Only one case of skeletal defect has been reported (Pujals, Figueras et al. 1989). The disease process itself for which Ciclosporin is indicated, makes these pregnancies high risk and subject to numerous potential problems, of which the most common is growth retardation. This latter problem is probably related to the mother's disease rather than to her drug therapy, but a contribution from Ciclosporin and corticosteroids cannot be excluded.

At present the recommendation is that Ciclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus. But as more cases of pregnancies whilst on Ciclosporin are reported, the safety profile of Ciclosporin use in pregnancy will improve. In this study, women will be advised against pregnancy during the trial period and advised about contraception. If a woman in the study were to fall pregnant during the study, she will be offered very close obstetric surveillance.

A number of articles have also discussed changes in Ciclosporin levels, usually a decline, during pregnancy (Burrows, Knight et al. 1994; Kozlowska-Boszko, Gaciong et al. 1998). Close monitoring of Ciclosporin levels is therefore necessary during pregnancy.

Nursing Mothers

Cyclosporine passes into breast milk. Mothers receiving treatment with Ciclosporin should not breast-feed.

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APPENDIX 5: ENL SEVERITY DATA COLLECTION SHEET

ENL data collection sheet for eventual scoring system

Experienced physician to score ENL as mild moderate or severe clinically on separate sheet.

Symptoms of ENL

How many days have you been feeling unwell for (this episode of ENL): _____ days

How unwell do you feel now (tick one face)?

Have you noticed....	NO	YES
Any new lumps on your skin?		
Any new sensory loss?		
Any new weakness in your muscles?		
Any new tingling?		
Any new pain in your joints?		
Any new pain in your bones?		
Any new pain in your testicles?		
Painful eyes?		
Any visual disturbance?		

Examination

Number of ENL lesions (circle): 0 1-5 6-20 >20

Inflammation in the ENL lesions (circle): None
Erythema and pain – function not affected
Erythema and pain – function affected
Erythema and pain – function affected plus ulceration

(If patient has previous records use comparison to previous VMT/ST testing):

VMT:	MRC=5	MRC=4	MRC=3	MRC<3
ST decreased in:	None	One nerve	Two nerve	≥ three nerves
Nerve tenderness:	None	Tender on palpation		Withdraws
Bone tenderness (shin):	None	Tender on palpation		Withdraws
Oedema (ankle, face, hands):	None	Present		Gross
Joint swelling:	None	Present		Affects function
Lymph nodes:	Normal	Enlarged and tender		
Testicles:	Normal	Tender (? Size)		
Temperature:	≤37.5°C	>37.5°C		level: _____
Proteinuria (by dipstick):	Negative	Positive		level: _____
Red eyes:	Yes	No		Ophthalmology diagnosis:

_____

APPENDIX 6: WHOQOL-BREF IN ENGLISH

WHOQOL–BREF

UK VERSION

Department of Mental Health

World Health Organisation

Geneva

For Office Use Only

	Equations for computing domain scores	Raw score	Transformed score	
			4-20	0-100
Domain 1	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17+ Q18 □ + □ + □ + □ + □ + □ + □	=		
Domain 2	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) □ + □ + □ + □ + □ + □	=		
Domain 3	Q20 + Q21 + Q22 □ + □ + □	=		
Domain 4	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 □ + □ + □ + □ + □ + □ + □ + □	=		

1

ABOUT YOU

Before you begin we would like you to answer a few general questions about yourself: by **circling** the correct answer or by **filling in the space provided**.

What is your gender? **MALE / FEMALE**

What is your date of birth? ____/___/_____. (day/month/year.)

What is the highest education you've received? **None at all**
Primary school
Secondary school
Tertiary

What is your marital status? **Single** **Separated**
Married **Divorced**
Living as married **Widowed**

Are you currently ill? **YES / NO**

If something is wrong with your health what do you think it is?
Please write your illness(s) or problem here:_____
_____

Instructions

This questionnaire asks how you feel about your quality of life, health and other areas of your life. **Please answer all the questions**. If you are unsure about which response to give to a question, **please choose the ONE** that appears most appropriate. This can often be your first response.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last two weeks**. For example, thinking about the last two weeks, a question might ask:

		Not at all	Not much	Moderately	A great deal	Completely
	Do you get the kind of support from others that you need?	1	2	3	4	5

You should **circle** the number that best fits how much support you got from others **over the last two weeks**. So you would circle the number 4 if you got a great deal of support from others as follows:

		Not at all	Not much	Moderately	A great deal	Completely
	Do you get the kind of support from others that you need?	1	2	3	4	5

You would circle the number 1 if you did not get any of the support that you needed from others in the last two weeks. Please read each question, assess you feelings, and **circle** the number on the scale for each question that gives the best answer for you.

2

		Very poor	Poor	Neither poor nor good	Good	Very good
1	How would you rate your quality of life?	1	2	3	4	5

		Very Dissatisfied	Dissatisfied	Neither Satisfied nor Dissatisfied	Satisfied	Very Satisfied
2	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things **in the last two weeks.**

		Not at all	A little	A moderate amount	Very much	An extreme amount
3	How much do you feel that pain prevents you from doing what you need to do?	1	2	3	4	5
4	How much do you need medical treatment to function in your daily life?	1	2	3	4	5
5	How much do you enjoy life?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
6	To what extent do you feel life to be meaningful?	1	2	3	4	5
7	How well are you able to concentrate?	1	2	3	4	5
8	How safe do you feel in your daily life?	1	2	3	4	5
9	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about **how completely** you experience or were able to do certain things **in the last two weeks**.

		Not at all	A little	Moderately	Mostly	Completely
10	Do you have enough energy for everyday life?	1	2	3	4	5
11	Are you able to accept your bodily appearance?	1	2	3	4	5
12	To what extent do you have enough money to meet your needs?	1	2	3	4	5
13	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

3

The following questions ask you to say **how good or satisfied** you have felt about various aspects of your life **over the last two weeks**.

		Very poor	Poor	Neither poor nor good	Good	Very good
15	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16	How satisfied are you with your sleep?	1	2	3	4	5
17	How satisfied are you with your ability to perform daily living activities?	1	2	3	4	5
18	How satisfied are you with your capacity for work?	1	2	3	4	5
19	How satisfied are you with yourself?	1	2	3	4	5
20	How satisfied are you with your personal relationships?	1	2	3	4	5
21	How satisfied are you with your sex life?	1	2	3	4	5
22	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24	How satisfied are you with your access to health services?	1	2	3	4	5
25	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to **how often** you have felt or experienced certain things **in the last two weeks**.

		Never	Seldom	Quite often	Very often	Always
26	How often do you have negative feelings, such as blue mood, despair, anxiety, depression?	1	2	3	4	5

Did someone help you to fill out this form? **YES / NO**

THANK-YOU FOR YOUR HELP

APPENDIX 7: AMHARIC WHOQOL-BREF

WHO QOL-BREF

ገለፃ

1. የለም
2. በትንሽ
3. መካከለኛ
4. በጣም
5. እጅግ በጣም

ኪው አ ኤል 1. የሕይወትዎን ጥራት ደረጃ እንዴት ይገመግሙታል?	1	2	3	4	5
ኪው አ ኤል 2. በጤናዎ ምን ያህል ረክተዋል?	1	2	3	4	5

የሚከተሉት ጥያቄዎች ባለፉት አራት ሳምንታት ህይወትዎ ላይ ያተኮሩ ናቸው

ኪው አ ኤል 3. ምን ያህል (የአካል)ህመም ማድረግ ካለብዎት ነገር እንዳስተጓጎልዎት ይሰማዎታል?	1	2	3	4	5
ኪው አ ኤል 4. ምን ያህል የህክምና ፅርዳታ የዕለት ተዕለት እንቅስቃሴዎ እንዳይጓደል ያስፈልግዎታል?	1	2	3	4	5
ኪው አ ኤል 5. ምን ያህል በህይወትዎ ይደሰታሉ?	1	2	3	4	5
ኪው አ ኤል 6. ምን ያህል ህይወትዎ ትርጉም አለው ብለው ይገምታሉ?	1	2	3	4	5
ኪው አ ኤል 7. አእምሮዎን ለማሰባሰብ ምን ያህል ዐቅም አለዎት?	1	2	3	4	5
ኪው አ ኤል 8. በዕለታዊ ህይወትዎ ምን ያህል ደህንነት ይሰማዎታል?	1	2	3	4	5
ኪው አ ኤል 9. ምን ያህል የአካል ጤንነት ይሰማዎታል?	1	2	3	4	5

1

የሚከተሉት ጥያቄዎች ምን ያህል በተመዋላ ሁኔታ ላለፉት አራት ሳምንታት አንዳንድ ነገሮች እንደተስማማምት በማወቅ ላይ ያተኩራል

ኪው አ ኤል 10. ለዕለት ተዕለት እንቅስቃሴም በቂ ጉልበት አለምት? 1 2 3 4 5

ኪው አ ኤል 11. የአካልምን ገጽታ በፀጋ ተቀብለዋል? 1 2 3 4 5

ኪው አ ኤል 12. ፍላጎትምን ለማሙዋላት በቂ ገንዘብ አለምት? 1 2 3 4 5

ኪው አ ኤል 13. ለዕለታዊ እንቅስቃሴም አስፈላጊዉን መረጃ ያገኛሉ? 1 2 3 4 5

ኪው አ ኤል 14. የመዝናኛ እንቅስቃሴዎች የማግኘት ችሎታም ምን ያህል ነው? 1 2 3 4 5

የሚከተሉት ጥያቄዎች ባለፉት አራት ሳምንታት የህይወት ገጠመኞችም ምን ያህል የእርካታ፤ የደስታ፤ወይም የጥሩ ስሜት እንዳደረብም የሚጠይቁ ናቸው

ኪው አ ኤል 15. ምን ያህል በእንቅልፍም ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 16. ዕለታዊ የኑሮ እንቅስቃሴምን በመምራት ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 17. በሥራ ችሎታም ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 18. በራስም ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 19. ከሰዎች ጋር ባለምት ግንኙነትም ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 20. በወሲባዊ ህይወትም ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 21. ከጓደኞችም በሚያገኙት ዕርዳታ ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 22. በመኖሪያ ቦታም ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 23. ለጤና አገልግሎት አቅርቦት ያለምት ርካታ ምን ያህል ነው? 1 2 3 4 5

ኪው አ ኤል 24. በመጓጓዣ በኩልስ? 1 2 3 4 5

ኪው አ ኤል 25. ከቦታ ወደ ቦታ በቀላሉ ይዘዋወራሉ? 1 2 3 4 5

የሚከተለው ጥያቄ ለምን ያህል በተደጋጋሚ አንዳንድ አዎንታዊ ስሜቶች፤ ለምሳሌ የቤተሰብ ደህንነት ወይም የጓደኛ ድጋፍ ወይም አሉታዊ ስሜቶች እንደ ደህንነት አልባ ዓይነት ተሰምቶዎት እንደሆነ ይጠይቃል

ኪው አ ኤል 26. ምን ያህል በተደጋጋሚ አሉታዊ ስሜቶች
እንደ መከፋት፤ ተስፋ መቁረጥ ጭንቀት
ወይም መደበት ደረሱብዎት ያውቃል? 1 2 3 4 5

ኪው አ ኤል 27. ምን ያህል በተደጋጋሚ ከአርስዎ በፊት
መጠለያው ይኖሩ የነበሩ ሰዎች በደንብ
እንደማይቀርቡዎት ይሰማዎታል? 1 2 3 4 5

ኪው አ ኤል 28. ትምህርት ለመማር ባጋጠመዎት ዕድል
ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 29. ሃይማኖትን ወይም በዓላትን ወይም የግል
እምነትን ለመከተል ባለው አመቺ ሁኔታ
ምን ያህል ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 30. ሥራ ለማግኘት ባለዎት ዕድል ምን ያህል
ረክተዋል? 1 2 3 4 5

ኪው አ ኤል 31. ወደ ሰብዓዊ መብት አስከባሪ ድርጅት
ለመቅረብ ምን ያህል ዕድል አግኝተዋል? 1 2 3 4 5

ኪው አ ኤል 32. በመጠለያው ባሉት የአድርና ሌሎች ማህበራት
ምን ያህል ይሳተፋሉ? 1 2 3 4 5

ኪው አ ኤል 33. በቀድሞ ሙያዎ ለመሥራት ምን
ያህል ችለዋል? 1 2 3 4 5

APPENDIX 8: SF-36 IN ENGLISH

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

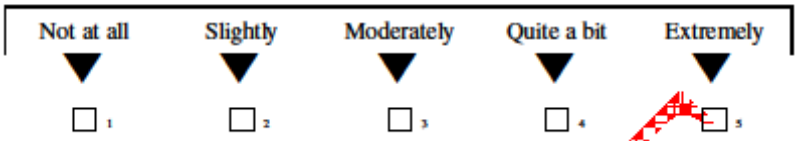
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

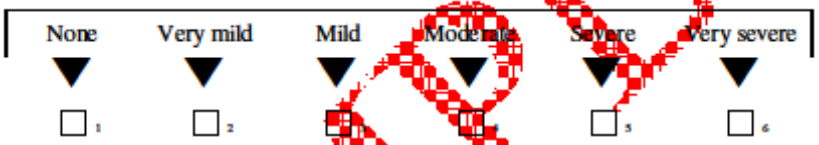
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

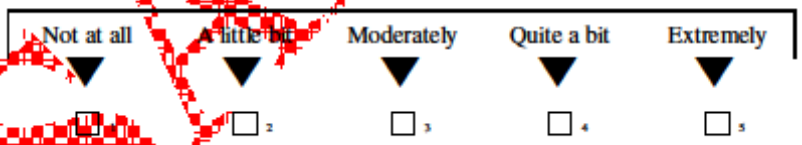
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much bodily pain have you had during the past 4 weeks?



8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

APPENDIX 9: AMHARIC SF-36

SF-36 የጤንነት መለኪያ ቅፅ
በህመምተኛ የሚሞላ

ስም (መጨረሻ፤ መጀመሪያ፤ መካከል፤ መነሻ)
መለያ ቁጥር
ሁኔታ

ትዕዛዝ፡- እያንዳንዱን ጥያቄ ከነኑ ያለውን ሳጥን ምልክት በማቅለም መልስ ይስጡ። መልሱን መለወጥ ከፈለጉ በፊት የሰጡትን መልስ እንዳለ ያጥፉት ለጥያቄው መልስ አርግጠኛ መሆን ካልቻሉ ካሉት መልሶች ውስጥ የተሻለውን ይምረጡ።

የዛሬው ቀን (ወር/ቀን/ዓ.ም.) ለእንድ ጥያቄ አንድ መልስ ብቻ ይኑሩ ☐☐ ☐☐ ☐☐

1. በአጠቃላይ ስለጤንነትም ምን ይላሉ?

እጅግ በጣም ጥሩ ☐ 1 በጣም ጥሩ ☐ 2 ጥሩ ☐ 3 ጤና የለኝም ☐ 4 ምንም አይል ☐ 5

2. አሁን ያለምት ጤንነት ከአመት በፊት ከነበረም ጋር ሲነፃፀር እንዴት ይገልፁታል?

በጣም የተሻለ ነው ☐1 በመጠኑ የተሻለ ነው ☐ 2 ያው ነው ☐ 3 በጣም ብሶብኛል ☐ 4 በመጠኑ ብሶብኛል ☐5

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3. የሚከተሉት ጥያቄዎች በየዕለቱ ስለሚያጋጥሙ የሥራ አይነት/ እንቅስቃሴ ይመለከታል አሁን ያለምት ጤንነትም እነዚህን ሥራዎች ከመሥራት ያግድምታል?

ተ.ቁ		በጣም አግዶኛል	በጥቂት አግዶኛል	በፍጹፁም አላገደኝም
a.	ጠንካራ እንቅስቃሴዎችን ለምሳሌ ሩጫ፤ከበድ ያለ ክብደት ማንሳት፤ከባድ ስፖርታዊ እንቅስቃሴ	☐ 1	☐ 2	☐ 3
b.	መካከለኛ እንቅስቃሴዎችን ለምሳሌ ጠረጴዛ መግፋት	☐ 1	☐ 2	☐ 3
c.	በዘንቢል የሞላ እቃ ማንሣት/ማንጠልጠል	☐ 1	☐ 2	☐ 3
d.	ብዙ ደረጃዎችን መውጣት	☐ 1	☐ 2	☐ 3
e.	አንድ ደረጃ መውጣት	☐ 1	☐ 2	☐ 3
f.	ማጎንበስ፤ መንበርከክ፤ቁጢጥ ማለት	☐ 1	☐ 2	☐ 3
g.	ከ1 ኪ.ሜ በላይ መጓዝ	☐ 1	☐ 2	☐ 3
h.	40 ሜትር መጓዝ	☐ 1	☐ 2	☐ 3
i.	120 ሜትር ያህል መጓዝ	☐ 1	☐ 2	☐ 3
j.	በራስም ገላ መታጠብ ወይንም ልብስ መልበስ	☐ 1	☐ 2	☐ 3

4. ባለፉት አራት ሳምንታት ምን ያህል ጊዜ ከአካልም ጤንነት የተነሳ የሚከተሉት ችግሮች ወይም ሌላ በአለታዊ እንቅስቃሴዎች ላይ አጋጥሞታል?

	ሁልጊዜ	አብዛኛው ጊዜ	አንዳንድ ጊዜ	ጥቂት ጊዜ	ምንም ጊዜ
a. ወትሮ በሥራ ላይ ወይም በሌላ ጉዳይ የማጠፋው ጊዜ ቀንሷል	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. መሥራት እየፈለክ መሥራት ከምችለው በታች እንድሰራ አድርጎኛል	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. አሁን እየሠራሁ ያለሁትን ሥራዎች እንዲሠራ ወስኖኛል	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. አሁን እየሠራሁ ያለሁትን እንዳልሠራ አግዶኛል /ምሳሌ ተጨማሪ ጉልበት ያስፈልገኛል/	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. ባለፉት አራት ሳምንታት ምን ያህል ጊዜ ከአእምሮ መደበት ወይም ጭንቀት የተነሣ የሚከተሉት ችግሮች ወይም ሌላ 01በዕለታዊ እንቅስቃሴ ላይ ችግር አጋጥሞታል ?

	ሁልጊዜ	አብዛኛው ጊዜ	አንዳንድ ጊዜ	ጥቂት ጊዜ	ምንም ጊዜ
a. ወትሮ በሥራ ላይ ወይንም በሌላ ጉዳይ የማጠፋው ጊዜ ቀንሷል	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. መሥራት እየፈለግሁ መሥራት ከምችለው በታች እንድሰራ አድርጎኛል።	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. ከወትሮ በተለየ በሥራ ላይ ግዴለሽነት	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. ባለፉት አራት ሳምንት ውስጥ ያለምት አካላዊ ወይንም ሥነልቦናዊ ጤንነት ምን ያህል ከቤተሰብ፣ ጓደኛ፣ጎረቤት ማህበረሰብ ውስጥ ያለምትን ማህበራዊ ግንኙነት ጎድቶታል ?

በፍፁም ☐ 1 በትንሹ ☐ 2 በመጠኑ ☐ 3 በጣም ☐ 4 እጅግ በጣም ☐ 5

7. ባለፉት አራት ሳምንታት የምን ያህል የሰውነት ስቃይ/ህመም አጋጥሞታል?

ምንም ☐ 1 በጣም ትንሽ ☐ 2 ትንሽ ☐ 3 በመጠኑ ☐ 4 ሐይለኛ ☐ 5 በጣም ሐይለኛ ☐ 6

8. ባለፉት አራት ሳምንታት የሰውነት ስቃይ/ህመም ምን ያህል የወትሮው ሥራዎን አስተጓጉሏል (የቤት ሥራ ወይንም ከቤት ውጭ)

በፍፁም ☐ 1 በጣም በጥቂቱ ☐ 2 በመጠኑ ☐ 3 በጣም ☐ 4 እጅግ በጣም ☐ 5

9. የሚከተሉት ጥያቄዎች ባለፉት አራት ሳምንታት ጀምሮ ምን እንደሚሰማዎትና ፣ጤንነትዎ እንዴት እንደነበር የሚያወሱ ናቸው። ለእያንዳንዱ ጥያቄ እንዴት እንደሚሰማዎት በጣም ሊገለፅ የሚችለውን መልስ ይምረጡ።

	ባለፉት አራት ሳምንታት ምን ያህል ጊዜ	ሁል ጊዜ	አብዛኛው ጊዜ	አንዳንድ ጊዜ	ጥቂት ጊዜ	ምንም ጊዜ
a.	በህይወትዎ ሙሉ እርካታ አግኝተዋል?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b.	በጣም ተበሳጭተው ግራ ግብት ብሎት ያውቃል?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c.	ምንም ነገር እስከማያስደስትዎት ድረስ አዝነው ወይም ተክዘው ያቃሉ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d.	ፍፁም ተረጋግተውና የውስጥ ሰላም ተሰምቶት ያውቃል ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e.	ፍፁም ጥንካሬ ተሰምቶዎት ያውቃል?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f.	ተደብተው /ተደብረው ያውቃሉ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g.	ፍፁም በነገሮች ተሰላችተው ያውቃሉ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h.	ደስተኛ ሆነው ያውቃሉ ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i.	ድካም ድካም ብሎዎት ያውቃል?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. ባለፉት አራት ሳምንታት ያሎዎት አካላዊ/ሥነልቦናዊ ጤንነት ምን ያህል ማህበራዊ ግንኙነቶውን ጎድተዋል? /ለምሳሌ ዘመድንና ጓደኛን ከመሸሽ አንጻር/

ሁል ጊዜ ☐ 1 አብዛኛው ጊዜ ☐ 2 አንዳንድ ጊዜ ☐ 3 ጥቂት ጊዜ ☐ 4 ምንም ጊዜ ☐ 5

11. የሚከተሉት አባባሎች ምን ያህል እውነት ወይም ሀሰት ናቸው ለእርስዎ?

		በጣም ትክክል	አብዛኛው ጊዜ እውነት	አላውቅም	በአብዛኛው ጊዜ ሀሰት	በፍፁም ሀሰት
a.	ከሌሎች ሰዎች በተለየ በቀላሉ በሽታ ይይዘኛል	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b.	እንደማንኛውም ሰው እኔም ጤነኛ ነኝ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c.	ጤናዬ እየባሰ እንደሚመጣ እጠብቃለሁ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d.	ፍፁም ጤነኛ ነኝ	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX 10: PATIENT DATA COLLECTION SHEET

Quality of Life Questionnaire - Patient information

Case number: _____ Date: _____

Age: ____ yrs Sex: M / F Patients Initials: __ __ __

Occupation: _____ Marital Status: _____

Can read and write (circle): YES NO

Educational Level (circle): None, primary school, Secondary, Tertiary

Residence: Rural or Urban
Who lives in house: _____

Leprosy History and Treatment:

How many years of Leprosy symptoms before diagnosis: _____
Type of leprosy diagnosed: TT/BT/BB/BL/LL PB/MB
Date of Diagnosis: _ _/ _ _/ _ _ _ _

MDT start date: _ _/ _ _/ _ _ _ _ RFT date: _ _/ _ _/ _ _ _ _

Months of MDT taken: _ _
Relapse(circle): Yes No

Type of leprosy reaction: Type 1/ENL/Neuritis/Silent Neuritis
Previous steroid treatment(circle): Yes/No
How many months of steroid therapy: _____
Hospital admission: No, in past, presently (how long: ___)

Disability grading now: Eyes: __, __ ; Hands___,___; Feet: ___,___

WHO Grade	0	1	2
Eyes	Normal	-	Reduced vision (unable to count fingers at 6 metres). Lagophthalmos.
Hands	Normal	Loss of feeling in the palm of the hand	Visible damage to the hands, such as wounds, claw hands or loss of tissue.
Feet	Normal	Loss of feeling in the sole of the foot	Visible damage to the foot, such as wounds, loss of tissue or foot drop.

Reason for attending hospital today: _____

Other: _____

APPENDIX 11: STUDY INFORMATION SHEET AND CONSENT FORM IN ENGLISH AND AMHARIC

All Africa Leprosy TB & Rehabilitation Centre (ALERT)

INFORMATION SHEET FOR PARTICIPANTS IN THE STUDY OF CICLOSPORIN TREATMENT IN LEPROSY REACTIONS

INVESTIGATOR: DR SABA LAMBERT

ALERT HOSPITAL AND LSHTM (London School of Hygiene and Tropical Medicine)

You are invited to participate in a study to test a new drug for leprosy reaction.

You are free to accept or to refuse. Before making your own decision, please listen to / read this information sheet which tells you about the study.

Purpose:

We are testing new treatments for Leprosy Reactions. Many leprosy patients have severe reactions in the skin or nerves. We treat these reactions with a drug called Prednisolone, but it does not always improve the skin and nerves, and it may cause some side effects. So we are looking for another drug that could work as well or better than Prednisolone and have fewer side effects. Ciclosporin acts in a similar way to Prednisolone. It is a suppressant of the immune system and has been used successfully in other diseases similar to leprosy. It has been used on a small Leprosy Reactions study here at ALERT a few years ago and the results were very encouraging. We would like to now do a larger comparative study.

The purpose of this study is to compare Ciclosporin and Prednisolone in the treatment of Leprosy Reactions. This is why we are inviting you to take part in the study.

Study design and procedures:

At the beginning of the study, all patients will have the same tests: a blood test (including an HIV test), a urine test, a stool test, a chest X-Ray if we suspect that you might have TB, and a skin biopsy. Women will undergo a pregnancy test at the start of the study and will be offered contraception during the duration of treatment. All patients will receive pre-test counselling at the ALERT VCT before undergoing an HIV test. Post-test counselling will also be offered. Patients found to be HIV positive or with active TB will be excluded from the study but will receive the standard ALERT treatment for leprosy and HIV at ALERT. The HIV test may be repeated during the study period if clinically indicated and you will receive counselling at the time.

During the study (1A), some patients will receive Ciclosporin and Prednisolone and others will receive Prednisolone only. You will be allocated randomly to one or other group so that we can compare the effects of the two medicines. Neither the doctor nor you, the patient will know which of the two treatments you are on. Only the pharmacist will know this. The medicines will be look similar and there will be similar number of pills. If you have already received Prednisolone in past, for this reaction, you will entered into Study 1B and given Ciclosporin directly.

The treatment will last for 20 weeks and the doses of medication will be gradually decreased. All patients will be followed up the same way at Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28 and 32 from the start date. On average a total of 7 blood tests and 2 skin biopsies will be taken during the 32 weeks study period. The biopsy will be 6mm in diameter maximum and will avoid the face.

Side effects, risks and discomforts:

Blood tests will be done regularly to detect some side effects. You may be at risk of developing infections or have other side effects on either the Prednisolone or Ciclosporin. From previous experience with Prednisolone (the drug which is the present standard treatment for leprosy reaction), serious side effects occur very rarely. Less than 5% of patients on Prednisolone experience side effects such as hypertension, abdominal discomfort, eye problems, and changes in weight.

Ciclosporin (the new drug) has been used for almost 30 years for various conditions. It has been used in leprosy in the last 10 years. Experience so far shows that it has similar but fewer and less severe side effects compared to prednisolone.
You will be questioned and monitored carefully at each visit to see if any of side effects occur; and if any arise you will be given advice and treatment as necessary.
Taking a blood sample may hurt for a short while and may cause a bruise but does not cause any serious problems. For the skin biopsy local anesthetic will be used, so the procedure will be painless but it will leave a small scar.
The risks to you as a patient are limited as you will receive optimum supervision and any side effects will be managed promptly. The risk for those patients who are in the study will not be more than those receiving standard leprosy reaction treatment.

Benefits:

The benefits to you are that during the study period you will receive the best treatment possible and attention of a dedicated physician. If any side effects arise, the cost of treatment will be covered by the Study. In case that you become seriously unwell for whatever reason, during the study period, you will be offered admission to ALERT hospital, and investigated and treated with all necessary care at the cost of the study.
Your travel expenses to attend the clinic for study purposes will be reimbursed. This will be Birr 15 for each visit if within Addis city, but may be more depending on the distance travelled.

Right to refuse or withdraw:

Taking part in the study is voluntary and you can decide to leave the study at any time for any reason. This will not affect your normal treatment from the hospital.
The reasons that you may be withdrawn from the study are:

a. If you wish to do so at any time
b. If you develop any serious adverse effects which will lead to the breaking of the code to see which treatment arm you are in.
c. Your HIV test becomes positive
d. If the study is interrupted for any major reason out-with our control

In all of the above cases you will continue to receive the standard treatment for Leprosy.

Confidentiality:

Information that we collect during the study will only be used by the people involved in this study for the purpose of this research or to perform quality control of this research. Your information will be treated with confidentiality and your name will not be published in any material concerning this study.
Some of these samples may be kept in the laboratory for further future studies.

Feed-back on research results:

Once the study is completed, all the information will be summarized and studied by doctors to see if Ciclosporin will be a good medication to use in the treatment of Leprosy Reactions. We will also inform you of the results of the study and how this will improve the future management of Leprosy Reactions.

Who to contact:

FOR ANY QUESTIONS OR PROBLEMS, CONTACT:

DR SABA LAMBERT	tel: 0911 824438
DR SHIMELIS DONI	tel: 0911 642060
DR DIGAFE TSEGAY	tel: 0911 407695
ALERT HOSPITAL	tel: 0113 211338

This protocol was reviewed and approved by the following Ethics Committees:
Ethics Committee of the London School of Hygiene and tropical Medicine
Ethics Committee of ALERT and AHRI (AAERC)
National Ethical Review Committee of Ethiopia.

Drug Administration and Control Authority (DACA)

The purpose of these ethics committees is to make sure that research participants are protected from harm. You can contact the ethics committee of Armauer Hansen Research Institute (AHRI)/ALERT at Addis Ababa, ALERT Hospital compound and the Ethiopian National Ethical Clearance committee at Addis Ababa Ethiopian Science and Technology Commission.

Study number: |__|__|__|__||__|__|__||__|__|__|

All Africa Leprosy TB & Rehabilitation Centre (ALERT)
CONSENT FORM FOR PARTICIPATION IN THE STUDY OF CICLOSPORIN IN THE TREATMENT OF LEPROSY REACTIONS

A. I -- - -- - - -- --- ---- ---- - -- - --- - - - --- - --- ---- - -- ---- - -- - -- - ---- --- ---- - ------ understand that doctors at ALERT Hospital and at the London School of Hygiene and Tropical Medicine are involved in research into new treatments for Leprosy Reactions. Ciclosporin acts in a similar way as the current drug in usage, Prednisolone. It is a suppressant of the immune system. This study will be comparing Ciclosporin and Prednisolone in the treatment of Leprosy Reactions, looking at their efficacy and side effect profiles. The study has been explained to me.

B. I confirm that I am 18 years old or above.

C. Depending on the type of reaction I am diagnosed, my treatment will be as follows:
NEW TYPE 1 REACTION or ENL: I shall be randomly assigned to a 4 month course of one of the treatment arms.
RECURRENT TYPE 1 REACTION: I shall be directly assigned to a 4 months course of Ciclosporin.
I agree to take all the tablets that I will be given.

D. I also agree to return for follow-up at 1, 2 and 3 months after the 3 months of treatment.

E. I understand that I will have to have regular blood tests to monitor for any side effects or new infections. The maximum amount of blood drawn at any time will be 9ml (this is the equivalent of 1 teaspoons). It is possible that I may experience some side effects as explained on the information sheet and that I will be treated for these freely and appropriately.

F. I agree to have 2 skin biopsies to monitor the effect of the drugs on the disease. I understand that this may leave a small scar.

G. Some of the samples taken (skin biopsy and blood) may be kept in a laboratory for up to 5 years to allow future studies. Please thick the box if you agree to follow up studies to be conducted on stored materials.

□ Yes, I agree □ No, I don't agree

H. Women only: I agree to undergo a pregnancy test and to attend Family Planning during the period of the study. If I become pregnant I may be withdrawn from the study but will continue on the standard treatment used in pregnancy.

I. I agree to be tested for HIV via VCT (Voluntary Counselling and Testing). If I am HIV positive I will be excluded from the study but will still receive the standard ALERT treatment for leprosy and HIV. HIV testing may be repeated during the study period if clinically indicated.

J. I understand that my name will not be revealed in any published material concerning this study. I understand that my notes will be treated with maximum confidentiality and will only be accessed by staff directly involved in the Study or the monitors of the Study.

K. I have received enough information about the study in a language I understand. I had the opportunity to discuss it and ask questions, and my questions have been answered to my satisfaction. I understand that participation is voluntary and that I am free to withdraw my consent at any time. I freely consent to participate in this research study and to allow treatment and tests to be performed on me as explained.

L. I understand that I can be requested anytime to terminate my participation in the trial if the need arises. I will be given full explanation of the reason and will still receive standard treatment.

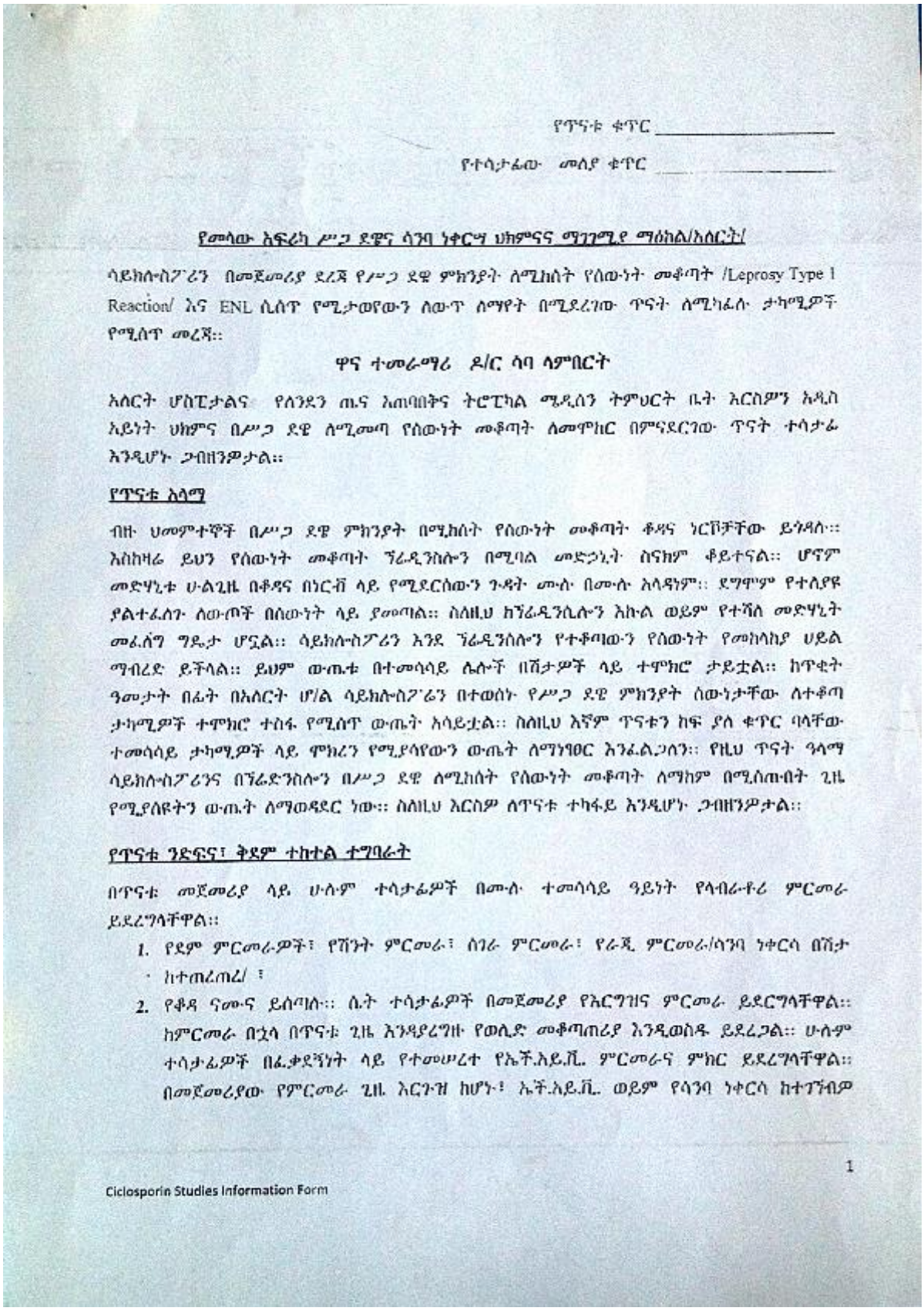
PATIENT'S SIGNATURE/MARK & DATE (European and Ethiopian)

_____ _____

DOCTOR'S or NURSE'S NAME & SIGNATURE & DATE

_____ _____

AMHARIC INFORMATION SHEET



የጥናቱ ቁጥር _____

የተሳታፊው መለያ ቁጥር _____

የመላው አፍሪካ ሥጋ ደዌና ሳንባ ነቀርሣ ህክምናና ማኅበሚያ ማዕከል/አሰርት/

ሳይክሎስፖሪን በመጀመሪያ ደረጃ የሥጋ ደዌ ምክንያት ለሚከሰት የሰውነት መቆጣት /Leprosy Type 1 Reaction/ እና ENL ሊሰጥ የሚታወየውን ለውጥ ለማየት በሚደረገው ጥናት ለሚካፈሉ ታካሚዎች የሚሰጥ መረጃ።

ዋና ተመራማሪ ዶ/ር ሳባ ላምበርት

አሰርት ሆስፒታልና የለንደን ጤና አጠባበቅና ትሮፒካል ሜዲሲን ትምህርት ቤት እርስዎን አዲስ አይነት ህክምና በሥጋ ደዌ ለሚመጣ የሰውነት መቆጣት ለመሞከር በምናደርገው ጥናት ተሳታፊ እንዲሆኑ ጋብዘንዎታል።

የጥናቱ አላማ

ብዙ ህመምተኞች በሥጋ ደዌ ምክንያት በሚከሰት የሰውነት መቆጣት ቆዳና ነርቮቻቸው ይጎዳሉ። እስከዛሬ ይህን የሰውነት መቆጣት ኘሬዲንሶሎን በሚባል መድኃኒት ስናክም ቆይተናል። ሆኖም መድሃኒቱ ሁልጊዜ በቆዳና በነርቭ ላይ የሚደርሰውን ጉዳት ሙሉ በሙሉ አላዳነም። ደግሞም የተለያዩ ያልተፈለጉ ለውጦች በሰውነት ላይ ያመጣል። ስለዚህ ከኘሬዲንሲሎን እኩል ወይም የተሻለ መድሃኒት መፈለግ ግዴታ ሆኗል። ሳይክሎስፖሪን እንደ ኘሬዲንሶሎን የተቆጣውን የሰውነት የመከላከያ ሀይል ማብረድ ይችላል። ይህም ውጤቱ በተመሳሳይ ሌሎች በሽታዎች ላይ ተሞክሮ ታይቷል። ከጥቂት ዓመታት በፊት በአሰርት ሆ/ል ሳይክሎስፖሪን በተወሰኑ የሥጋ ደዌ ምክንያት ለውነታቸው ለተቆጣ ታካሚዎች ተሞክሮ ተስፋ የሚሰጥ ውጤት አሳይቷል። ስለዚህ እኛም ጥናቱን ከፍ ያለ ቁጥር ባላቸው ተመሳሳይ ታካሚዎች ላይ ሞክረን የሚያሳየውን ውጤት ለማነባበር እንፈልጋለን። የዚህ ጥናት ዓላማ ሳይክሎስፖሪንና በኘሬድንሶሎን በሥጋ ደዌ ለሚከሰት የለውነት መቆጣት ለማከም በሚሰጡበት ጊዜ የሚያሰዩትን ውጤት ለማወዳደር ነው። ስለዚህ እርስዎ ለጥናቱ ተካፋይ እንዲሆኑ ጋብዘንዎታል።

የጥናቱ ንድፍና፣ ቅደም ተከተል ተግባራት

በጥናቱ መጀመሪያ ላይ ሁሉም ተሳታፊዎች በሙሉ ተመሳሳይ ዓይነት የላብራቶሪ ምርመራ ይደረግላቸዋል።

1. የደም ምርመራዎች፣ የሽንት ምርመራ፣ ስባራ ምርመራ፣ የራጂ ምርመራ/ሳንባ ነቀርሳ በሽታ ከተጠረጠረ/ ፣
2. የቆዳ ናሙና ይሰጣሉ። ሴት ተሳታፊዎች በመጀመሪያ የእርግዝና ምርመራ ይደርግላቸዋል። ከምርመራ በኋላ በጥናቱ ጊዜ እንዳያረግዙ የወሊድ መቆጣጠሪያ እንዲወስዱ ይደረጋል። ሁሉም ተሳታፊዎች በፈቃደኝነት ላይ የተመሠረተ የኤች.አይ.ቪ. ምርመራና ምክር ይደረግላቸዋል። በመጀመሪያው የምርመራ ጊዜ እርጉዝ ከሆኑ፣ ኤች.አይ.ቪ. ወይም የሳንባ ነቀርሳ ከተገኘብዎ

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Ciclosporin Studies Information Form

በጥናቱ አይሳተፉም። ሆኖም አስፈላጊው ህክምና ለኤች.አይ.ቪ.ም ሆነ የሳንባ ነቀርሳ በሽታ የአሰርት መመሪያ በሚፈቅደው መሠረት ይሰጥሥታል።

በጥናቱ ወቅት የተመሰኑ ህመምተኞች <u>ሳክሲ-ስፖሪንና ፕሬዲንሲሶን</u> ይሰጣቸዋል። የቀሩት ደግሞ <u>ፕሬዲንስሶን</u> ብቻ ያገኛሉ። ስለዚህ ከእኛህ ሁለት ቡድኖች በአንዱ ውስጥ ይመደባሉ። ይህም እኛ በሁለቱ መድሃኒቶች የሚታየውን ውጤት በማወዳደር በምናደርገው ጥናት ይረዳናል። ጥናቱ 20 ሳምንት ይፈጃል። የመድሃኒቱ አወሳሰድ መጠንም ቀስ በቀስ እየተቀነሰ ይሄዳል። ለሁሉም በሽተኞች በተመሳሳይ አይነት ከመጀመሪያው ቀን ጀምሮ በ2ተኛው፣ በ4ተኛው፣ በ6ተኛው፣ በ8ተኛው፣ በ12ተኛው፣ በ16ተኛ ው፣ በ20ኛው፣ በ24ተኛው፣ በ28ተኛው እና 32ተኛው፣ ሳምንት የክትትል ምርመራ ይደረግልዎታል። በጠቅላላው በ3ፉቱ ሳምንታት ውስጥ በአማካይ 7 ጊዜ የደም ምርመራና ሁለት ጊዜ የቆዳ ናሙና ይሰጣሉ።።።

<u>ተጓዳኝ፣ ችግሮች፣ ጉዳቶችና አለመመቸት</u>

መድሃኒቱ በሰውነት ላይ የሚያመጣውን የማያስፈልግ ለመጥየ/ጉዳት/ ለመቆጣጠር በተለያየ ጊዜ የደም ምርመራ ይወስዳል። በሳይክሎስፖሪን ወይም ፕሬዱንስሶን ምክንያት ሰፊ የሆኑ ለሌሎች ተላላፊ በሽታዎች ሊጋለጡ ይችላሉ። ፕሬዲኒስሶን የተባለውን መድሃኒት ለሥጋ ደዌ ህክምና ቀደም ብለንና አሁንም እየተጠቀምንበት ነው። ቀደም ብሎ በመድሃኒቱ ሲታከሙ ከቆዩት ታካሚዎች ያገኘነው ልምድ ፕሬዲኒሶን ለህይወት አስጊ የሆኑ ችግሮችን አብዛኛውን ጊዜ አያመጣም። ስለዚህ መድሃኒቱን ከወሰዱ ታካሚዎች መሃል አምስት በሙሉ የሚሆኑትን ግን አንደ ደም ግፊት የሆድ ህመም የአይን ችግር ክብደት መጨመር ሊታይባቸው ይችላል። እንዲሁም አዲስ መድሃኒት (Ciclosporin) ከ30 ዓመታት ለተለያዩ ህመሞች ስንጠቀምበት ቆይተናል። በተጨማሪም ለሰጋ ደዌ ታካሚዎች ካለፉት 10 ዓመታት ጀምሮ እየተጠቀምንበት ነው። እስካሁን ከተገኘው ልምድ የሚያመጣው ጉዳት ከፕሬዲኒሶን በጣም ዝቅ ያለና በጣም ጥቂት እንደሆነ ተረጋግጧል።

ለክትትል በሚመጡበት ጊዜ ያጋልባት እነዚህ ችግሮች እንዳሉና እንደሌሉ ለማወቅ በጥንቃቄ የተለያዩ ጥያቄዎች ይጠየቃሉ። ችግሩም ካለ ምክርና አስፈላጊ ህክምና ይደረግልዎታል። የህክምናዎ ወጪ በሙሉ በጥናቱ ይከፈልልዎታል።

በጥናቱ ወቅትም በምንም ዓይነት ምክንያት በጤና ከታመሙና አስፈላጊ ሆኖ ከተገኘ በአሰርት ሆ/ል ተኝተው ይታከማሉ። የሚያስፈልግዎ የህክምና ወጪ በሙሉ ይሸፈንልዎታል።

የደም ምርመራ በሚወሰድ ጊዜ ትንሽ ሊያምዎና የተወጋው ቦታ ሊያብጥ ሊቁላ ይችላል ሆኖም ምንም ጉዳት ሳያደርስ በትንሽ ደቂቃ መሰጥ እንደሚጠፋ እንደሚድን የታወቀ ነው።

የቆዳ ናሙና ሲወሰድ እንዳያምዎ ማደንዘዣ ይሰጥሥታል ሆኖም ናሙና የተወሰደበት ቦታ ሊቆስልና ትንሽ ጠባሳ ሊኖረው ይችላል።

ከፍተኛ ጥንቃቄ የተሞላበት ክትትል ህክምና ስለሚደረግልዎት ሊደርሱ የሚችሉት ችግሮችና ጉዳቶች በጣም የተወሰኑ ናቸው። ችግሮቹም ከተከሰቱ ወዲያውኑ አስፈላጊ ምርመራና ህክምና ይደረግልዎታል። በጥናቱ በሚሳተፉ ሰዎች ሊከሰት የሚችለው ጉዳት (በጥናት ካልተሳተፉት) መደበኛ የህክምና አገልግሎት ከሚሰጣቸው ሰዎች የማይለዋ አይደለም።

<u>የሚገኝ ጥቅም</u>በጥናቱ ጊዜ በጣም ጥራት ያለው ህክምናና እንክብካቤ በመደቻው የተዋጣላቸው ሀኪሞች ይሰጥዎታል።

ለህክምናው ክትትል በሚመላለሱበት ጊዜ የመጓጓዣ ወጪዎን በመሉ ይከፈልዎታል።

<u>ፈቃደኛ ያለመሆንና ከጥናቱ አቋርጦ የመውጣት መብት</u>

በዚህ ጥናት መሳተፍ በፍቃደኝነት ላይ የተመሰረተ ነው ስለዚህ በማንኛውም ጊዜ በምንም አይነት ምክንያት ከጥናቱ ሰመውጣት ይችላሉ። ከጥናቱ መውጣትም በአሰርት ሆ/ል የሚሰጥዎ ማንኛውም አይነት ህክምና አይጓደልብዎትም።

<u>ከጥናቱ አቋርጠው ሰውጡ የሚችሉባቸው ምክንያቶች</u>

ሀ/ በራስዎ ፈቃድ መወጣት ከፈለጉ

ለ/ በመድሃኒቶቹ ምክንያት ከፍተኛ የሆነ ጉዳት የሚያስከትል ሁኔታ ከተፈጠረና የሚወስዱት የትኛው መድሃኒት መሆኑን ሰማወቅ የሚሰጥር ቁጥሩን ገልጦ ማየት የሚያስገድድ ሁኔታ ከተፈጠረ

ሐ/ በጥናቱ መሳል እያሉ የኤች.አይ.ቪ. በሽታ ከተገኘብዎ

መ/ ከቁጥጥር ውጭ በሆነ ሁኔታ ጥናቱ ከተቋረጠ

ከላይ በተጠቀሱት በየትኛው ምክንያት ከጥናቱ ቢወጡም በአሰርት በዙሉ የሚደረግልዎ ህክምና አንዳስ ይቀጥላሉ።

<u>ሚስጥር አጠባበቅ</u>

በጥናቱ ወቅት የሚሰበሰቡ መረጃዎች በሙሉ በጥናቱ ላይ ተካፋይ የሆኑ ተመራማሪዎች ብቻ ተጠቅመው ለጥናቱ አላማ ያውሉታል። የሚሰጡን መረጃዎች በሙሉ በሚስጥር ይጠበቃሉ። የጥናቱ ውጤት በጽሁፍ በሚታተምበት ጊዜ ስምዎ አይገለጥም።

ለምርምሩ ከሰጡት የተወሰነው የደም ሆነ የቆዳ ናሙናዎች በላብራቶሪ ተተምጠው ቀጣይ ምርምር ይካሄድባቸዋል።

በጥናቱ ውጤት ላይ ተመስርቶ የሚሰጥ ምላሽ

ጥናቱ ከተጠናቀቀ በኋላ የተገኙት መረጃዎች መሉ በመሉ ተጠናቅረው ሳይክሎስፖሪን በስጋ ደዌ ምክንያት ለሚከሰት የሰውነት መቆጣትን ለማከም ጥሩ መድሃኒት እንደሆነ ይጠናል። ውጤቱንም በስፊው ይገልጽልዎታል። በተጨማሪም ለወደፊቱ በስጋ ደዌ ምክንያት የሚመጣውን የሰውነት መቆጣት ለመቆጣጠር የሚቻልበትን የህክምና ዘዴ ያሻሽላል።

ተጨማሪ ጥያቄ ቢኖርዎ ማግኘት የሚገባዎ ሰዎች

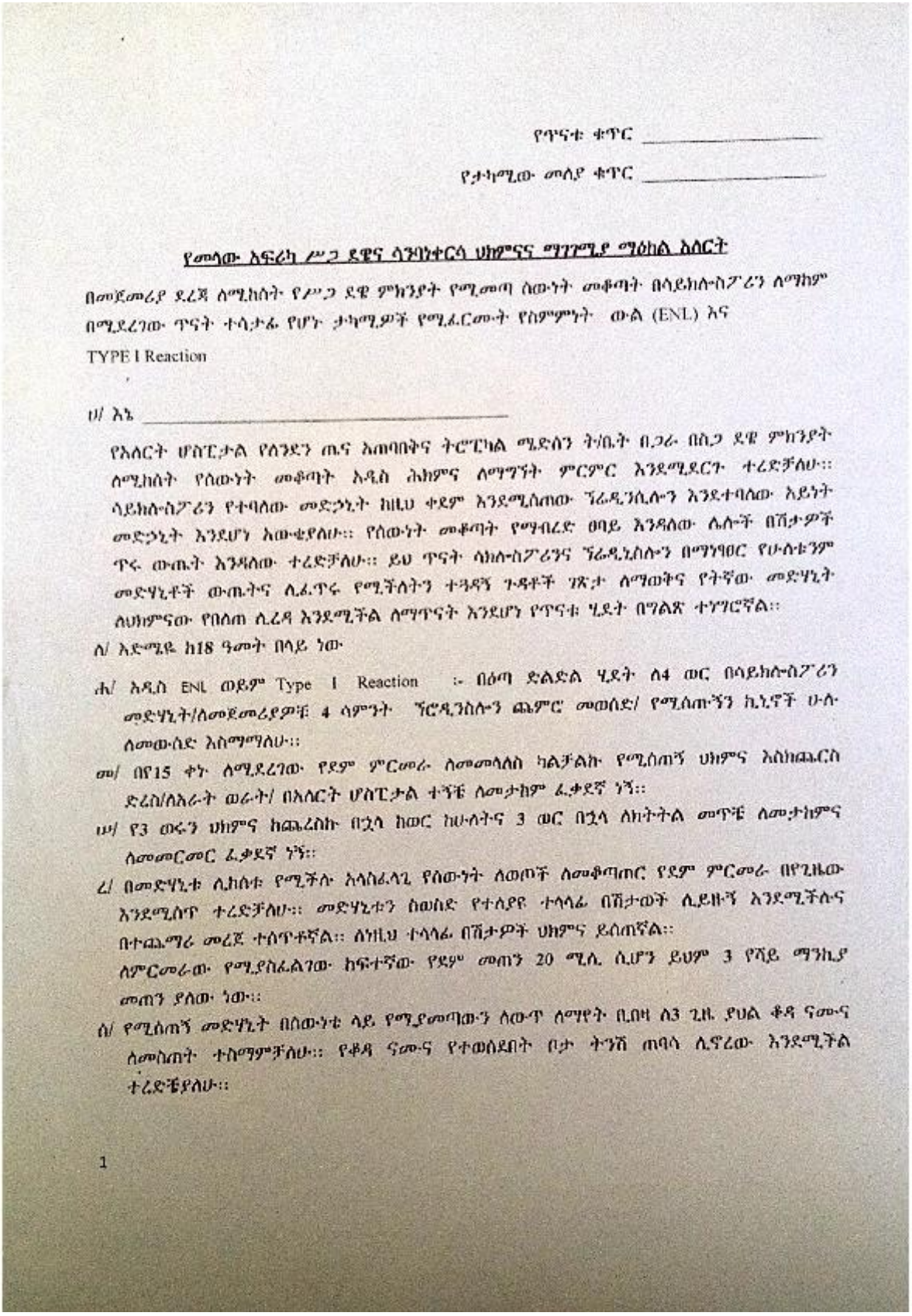
1. ዶ/ር ሳባ ላምበርት ዋና ተመራማሪ 09 11 82 44 38
2. ዶ/ር ድጋፌ ፀጋዬ የጥናቱ ሀኪም 09 11 40 76 95
3. ዶ/ር ሽመልስ ንጉሴ የጥናቱ ሀኪም 09 11 64 20 60

የዚህ ጥናት ጥንቅር ቅጂ በሚከተሉት የሥነ ምግባር ኮሚቴዎች ከተገመገመ በኋላ ተቀባይነት አግኝቶ ፀድቋል።

- የሰንደን ጤና እጠባበቅና ትሮፒካል ሜድስን ት/ቤት ስነ ምግባር ኮሚቴ
- የአህራና/አሰርት ኢንስቲትዩት ስነ ምግባር ኮሚቴ
- በኢትዮጵያ ሳይንስና ቴክኖሎጂ ኮሚሽን ስነ ምግባር ኮሚቴ

የሥነ ምግባር ኮሚቴዎች አላማ በጥናቱ ተሳታፊ የሆኑ ታካሚዎችን ሰብዓት እንዳይጋለጡ መጠበቅ ነው። እነዚህን ኮሚቴዎች ማግኘት ከፈለጉ
በአሰርት ሆስፒታል ግቢና በሳይንስና ቴክኖሎጂ ኮሚሽን ግቢ ውስጥ ይገኛሉ።

AMHARIC CONSENT FORM



የጥናቱ ቁጥር _____

የታካሚው መለያ ቁጥር _____

የመላው አፍሪካ ሥጋ ደዌና ሳንባነቀርሳ ህክምናና ማሠልጠኛ ማዕከል አሰርት

በመጀመሪያ ደረጃ ለሚከሰት የሥጋ ደዌ ምክንያት የሚመጣ ስውነት መቆጣት በላይክሎስፖሪን ለማከም በሚደረገው ጥናት ተሳታፊ የሆኑ ታካሚዎች የሚፈርሙት የስምምነት ውል (ENL) እና

TYPE I Reaction

ሀ/ እኔ _____

የአሰርት ሆስፒታል የሰንደን ጤና አጠባበቅና ትሮፒካል ሜድሰን ት/ቤት በጋራ በስጋ ደዌ ምክንያት ለሚከሰት የስውነት መቆጣት አዲስ ሕክምና ለማግኘት ምርምር እንደሚደርጉ ተረድቻለሁ። ላይክሎስፖሪን የተባለው መድኃኒት ከዚህ ቀደም እንደሚሰጠው ኘሬዲንሲሎን እንደተባለው አይነት መድኃኒት እንደሆነ አውቂያለሁ። የስውነት መቆጣት የማብረድ ፀባይ እንዳለው ሌሎች በሽታዎች ጥሩ ውጤት እንዳለው ተረድቻለሁ። ይህ ጥናት ላክሎስፖሪንና ኘሬዲኒሶሎን በማነፃፀር የሁለቱንም መድሃኒቶች ውጤትና ሊፈጥሩ የሚችሉትን ተጓዳኝ ጉዳቶች ገጽታ ለማወቅና የትኛው መድሃኒት ለህክምናው የበለጠ ሊረዳ እንደሚችል ለማጥናት እንደሆነ የጥናቱ ሂደት በግልጽ ተነግሮኛል።

ለ/ እድሜዬ ከ18 ዓመት በላይ ነው

ሐ/ አዲስ ENL ወይም Type I Reaction :- በፅጣ ድልድል ሂደት ለ4 ወር በላይክሎስፖሪን መድሃኒት/ለመጀመሪያዎቹ 4 ሳምንት ኘሮዲንሲሎን ጨምሮ መወሰድ/ የሚሰጠኝን ኪኒኖች ሁሉ ለመውሰድ እስማማለሁ።

መ/ በየ15 ቀኑ ለሚደረገው የደም ምርመራ ስመመላለስ ካልቻልኩ የሚሰጠኝ ህክምና እስከጨርስ ድረስ/ለአራት ወራት/ በአሰርት ሆስፒታል ተኝቼ ለመታከም ፈቃደኛ ነኝ።

ሠ/ የ3 ወሩን ህክምና ከጨረስኩ በኋላ ከወር ከሁለትና 3 ወር በኋላ ለክትትል መጥቼ ለመታከምና ለመመርመር ፈቃደኛ ነኝ።

ረ/ በመድሃኒቱ ሊከሰቱ የሚችሉ አላስፈላጊ የሰውነት ለወጦች ለመቆጣጠር የደም ምርመራ በየጊዜው እንደሚሰጥ ተረድቻለሁ። መድሃኒቱን ስወሰድ የተለያዩ ተላላፊ በሽታወች ሊይዙኝ እንደሚችሉና በተጨማሪ መረጀ ተሰጥቶኛል። ለነዚህ ተላላፊ በሽታዎች ህክምና ይሰጠኛል።

ለምርመራው የሚያስፈልገው ከፍተኛው የደም መጠን 20 ሚሊ ሲሆን ይህም 3 የሻይ ማንኪያ መጠን ያለው ነው።

ሰ/ የሚሰጠኝ መድሃኒት በሰውነቱ ላይ የሚያመጣውን ለውጥ ለማየት ቢበዛ ለ3 ጊዜ ያህል ቆዳ ናሙና ለመስጠት ተስማምቻለሁ። የቆዳ ናሙና የተወሰደበት ቦታ ትንሽ ጠባሳ ሊኖረው እንደሚችል ተረድቼያለሁ።

1

ሸ/ የምሰጠው ናሙና ማለትም/የቆዳና የደም/ ቀጣይ ምርምር ለማካሄድ እሰክ አምስት አመት ድረስ በሳብራቶሪ ሊቀመጥ እንደሚችል ተነግሮኛል። አክሎም በሚቀመጠው ናሙናው ላይ ቀጣይ ምርምር እንዲከሄድ ፈቃደኛ መሆንና አለመሆንዎን በሚቀጥለው ሳጥን ውስጥ ምልክት ያድርጉ።

☐ አዎን አስማማለሁ ☐ የለም አልስማማም

ቀ/ ለሴት ታካሚዎች የእርግዝና ምርመራ እንዲደረግልኝና የወሲድ መቆጣጠሪያ በክሎናው ወቅት ለመውሰድ ተስማምቻለሁ። እርጉዝ ከሆንኩ ከምርምሩ እንደምወጣ ተነግሮኛል። ሆኖም ሌላ አስፈላጊው ህክምና በአሰርት ሆስፒታል በኩል እንደሚቀጥልልኝ አውቃለሁ።

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2

APPENDIX 12: STANDARD OPERATING PROCEDURES

CnT1R and CnENL

STANDARD OPERATING PROCEDURES

Recruitment

Laboratory

Physiotherapy

Physician review

Pharmacy

Follow up

Adverse Events

Data Management

CONTENTS

Profile of study T1RA
Profile of study T1RB
Profile of study ENLA
Profile of study ENLB

Patient Work Flow

RECRUITMENT:
- Eligibility
- Informed Consent
- Assigning patient a study number
- Completing study register
- Starting a PRF

LABORATORY INVESTIGATIONS:
- Bloods
- Urine
- Stool
- BI
- Biopsy
- VCT and HIV testing

PHYSIOTHERAPY:
- Physiotherapy for VMT/ST assessment
- Clinical Severity Score for T1R

PHYSICIAN REVIEW:
- History at registration
- Examination at registration
- Results
- Management

PHARMACY:
- Referral to Pharmacy
- Randomisation and allocation of treatment
- Treatment record
- Treatment dispensing

Transport payment and Follow up appointment registered
Other information collected at registration: Quality of Life Questionnaire
Check list on recruitment

STORING SOURCE DOCUMENTS AND PRF

FOLLOW-UP VISITS
- Follow-up schedule
- Treatment regimens for T1R and ENL
- Welcoming patient
- Checking register and marking visit
- Obtaining PRF and organising planned investigations
- Nurse's review: weight BP pulse
- Laboratory sample collected
- Physiotherapy assessment
- Physician's history and examination
- Referral to Pharmacy
- Treatment provided
- Appointment date registered
- Transport allowance provided
- All results gathered and attached to PRF
- CRF storage

Using additional Prednisolone

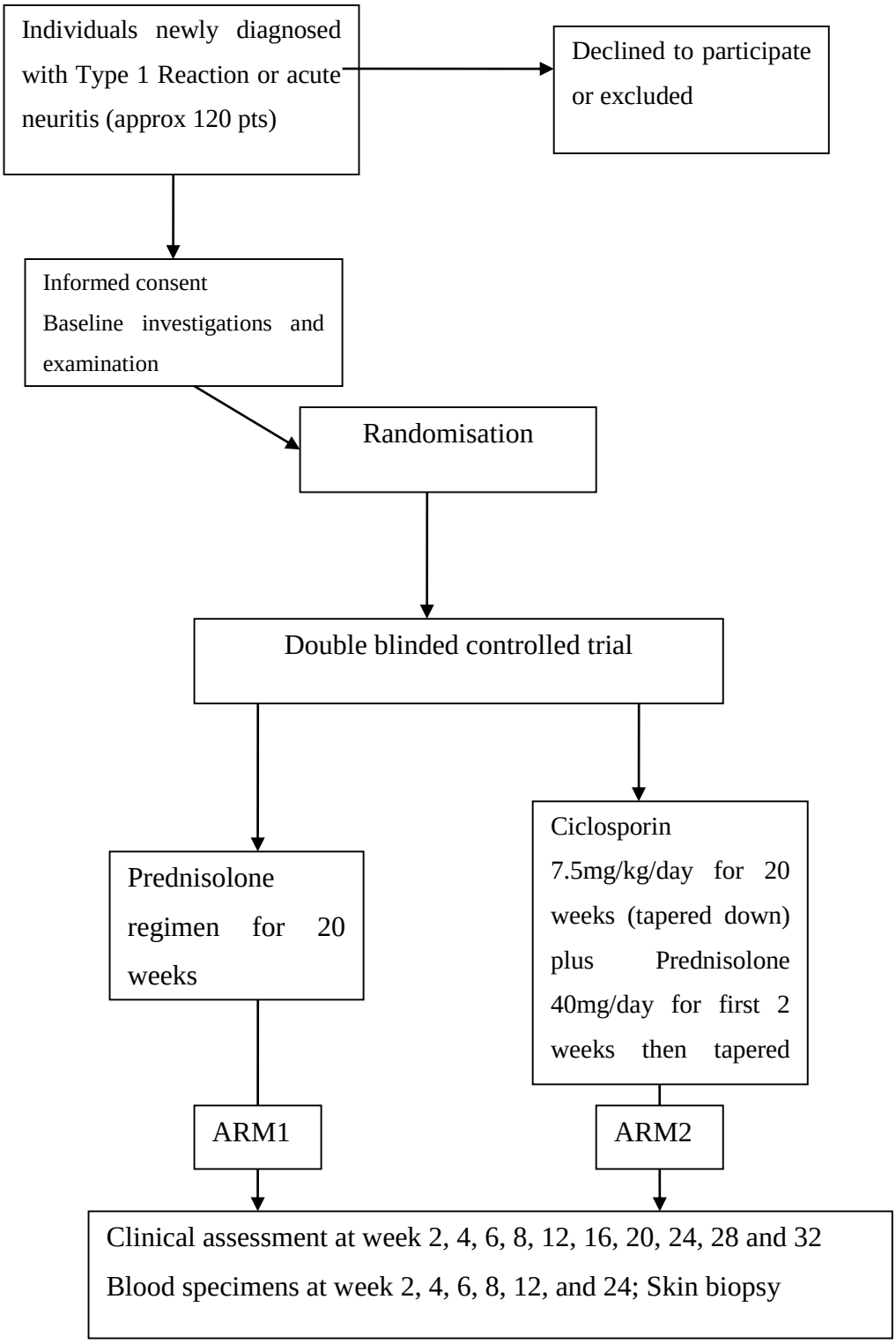
Adverse events
- Prednisolone side effects
- Ciclosporin side effects
- Ciclosporin contra-indications
- Drug interactions
- Laboratory monitoring

- Managing clinical symptoms
- Serious adverse events
- Hospitalization criteria

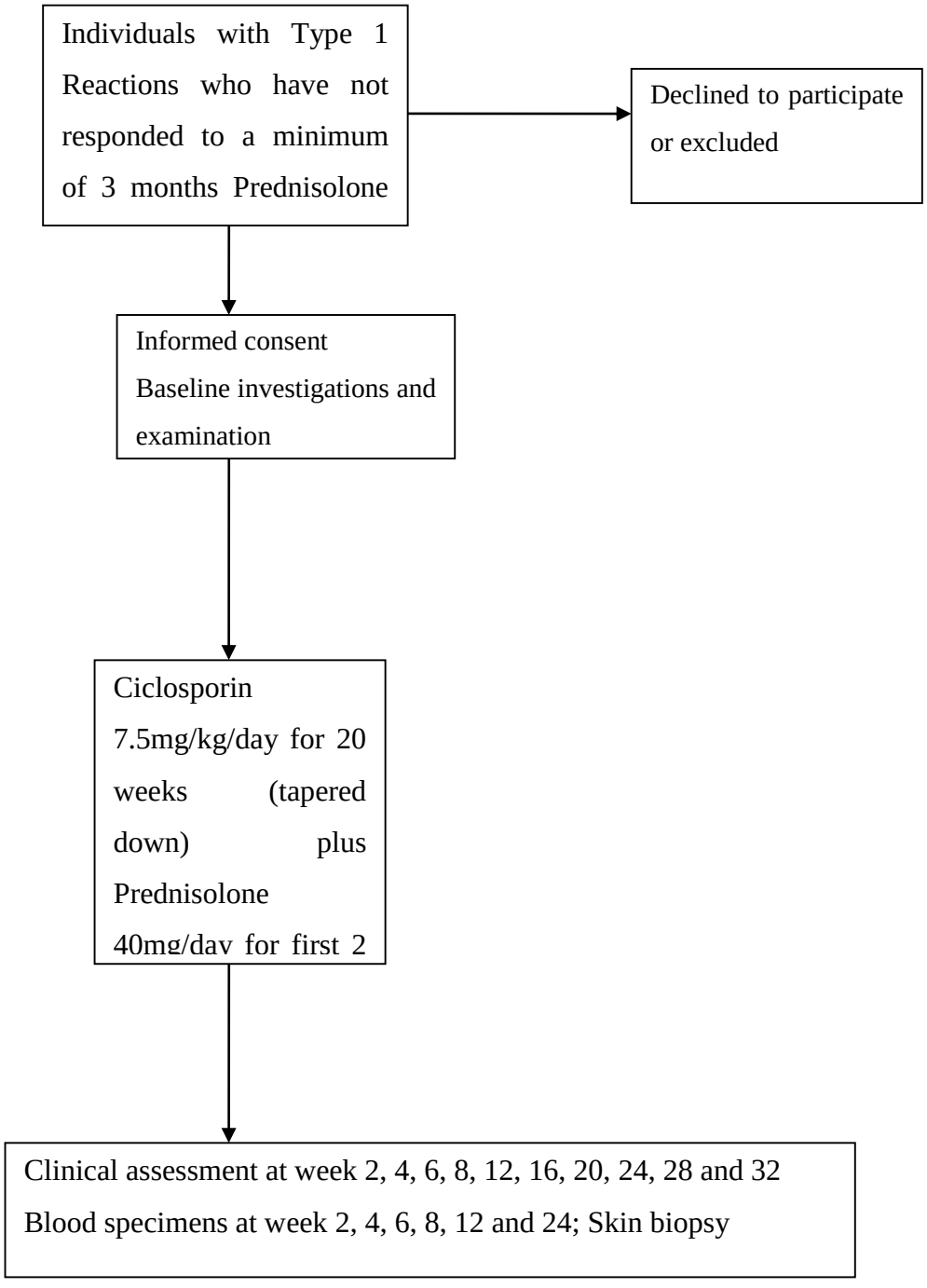
Un-blinding procedure
Late clinic attendance
Unscheduled clinic attendance

DATA MANAGEMENT
- Storage of PRF
- CRF recording and storage
- Data entry

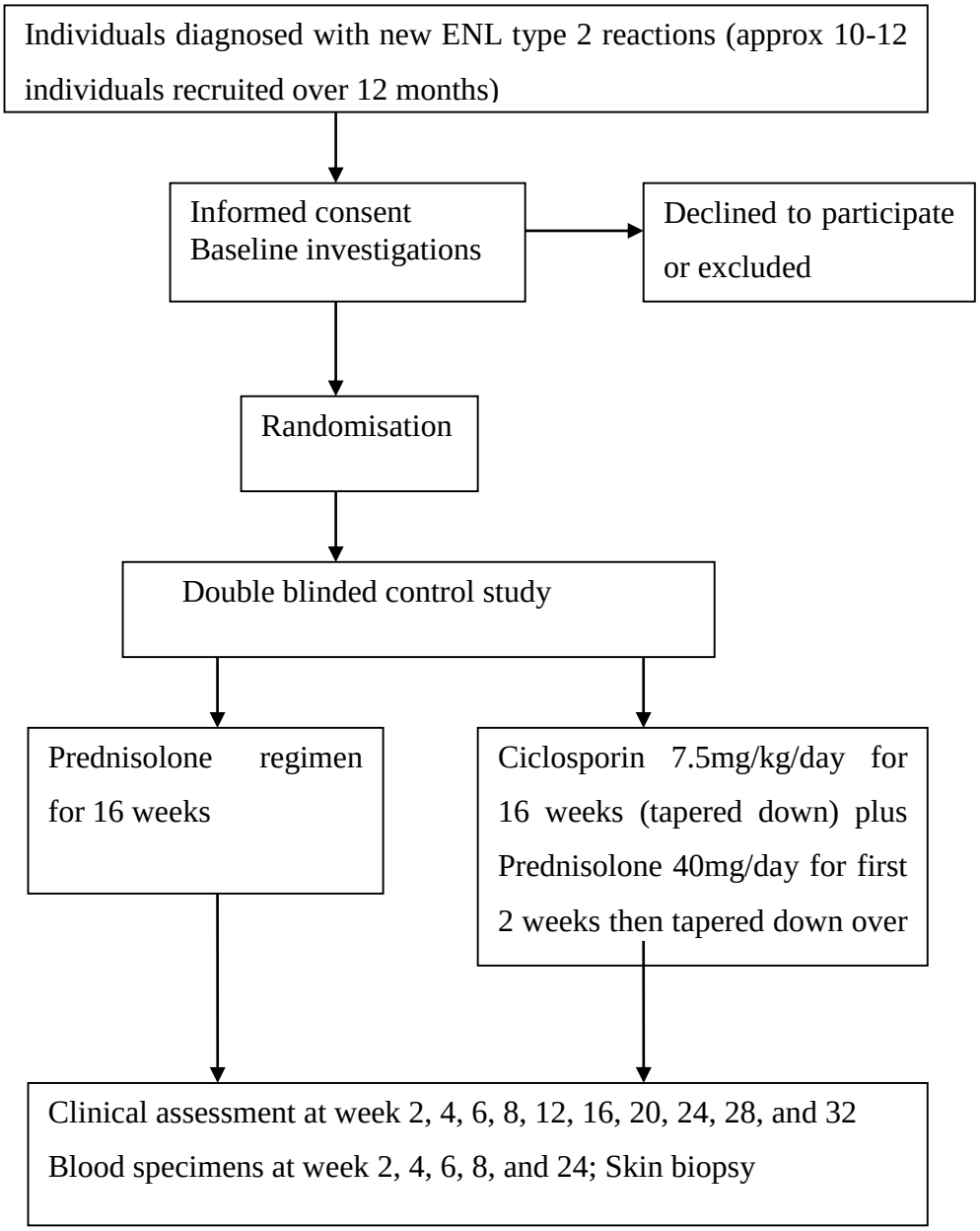
Profile of Study T1RA: A randomised controlled trial comparing the treatment of Type 1 reactions with Ciclosporin or Prednisolone.



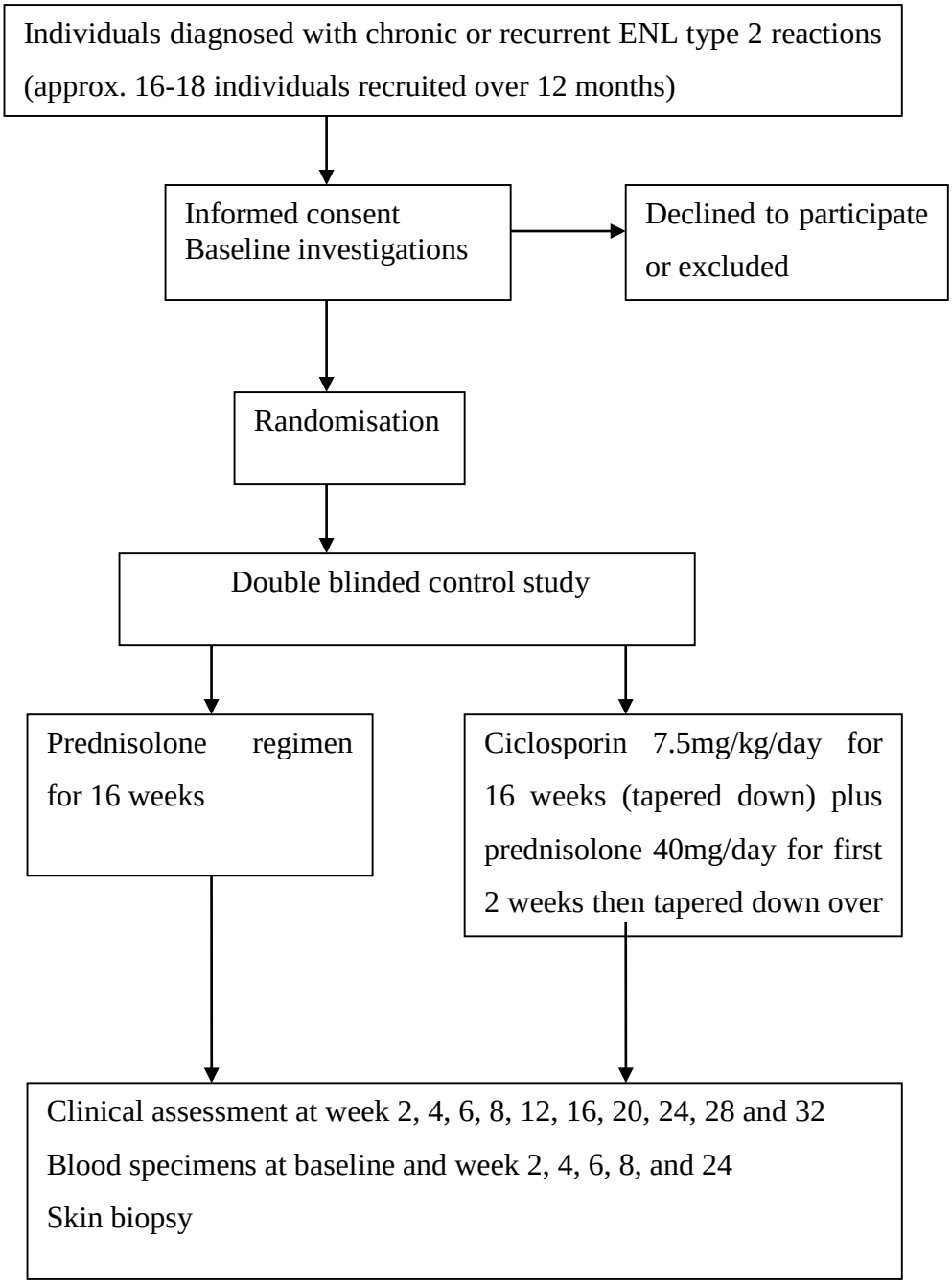
Profile of Study T1RB: A pilot study assessing the efficacy of Ciclosporin in steroid resistant Type 1 reactions.



Profile of Study ENLA: A pilot study randomizing patients with new acute ENL to treatment either with Ciclosporin or Prednisolone.



Profile of Study ENLB: A pilot study randomizing patients with recurrent or chronic ENL, already on Prednisolone treatment with Ciclosporin or additional Prednisolone.



Patient Work Flow on recruitment

1. Patient identified at Red Medical Clinic and registered
2. Patient informed about study, and recruited with consent
3. Patient sent for outstanding Laboratory investigations and skin biopsy
4. Patient sent to Physiotherapy for ST/VMT
5. All results gathered
6. Full history and examination by study physician
7. Patient referred to Pharmacist for treatment allocation and treatment distribution
8. Patient given review date

RECRUITMENT PROCESS AT RMC

Summary of studies:

There are four studies in this project:

Study T1RA and T1RB are for Type 1 reactions.

Study ENLA and ENLB are for ENL reactions.

Study T1RA: A randomised controlled trial comparing the treatment of Type 1 reactions with Ciclosporin or Prednisolone.

Study T1RB: A pilot study assessing the efficacy of Ciclosporin in steroid resistant Type 1 reactions

Study ENLA: A pilot study randomizing patients with new acute ENL to treatment either with Ciclosporin or Prednisolone.

Study 2B: A pilot study randomizing patients with recurrent or chronic ENL, already on Prednisolone treatment with Ciclosporin or additional Prednisolone.

Study codes and patient numbers:

	New	Recurrent
Type 1 reaction	CnT1RA n=120	CnT1RB n=20
ENL	CnENLA n=12	CnENLB n=20

Eligibility (Fill in Recruitment Form)

Entry criteria

All Patients must be:
Aged 16-65
Weigh more than 30Kg
HIV negative
With either a Type 1 Reaction or ENL

Exclusion criteria

Anyone unwilling or unable to give consent.
Individuals with severe active infection such as tuberculosis or HIV/ AIDS.
Individuals with severe inter-current disease (cardiac, hepatic or renal disorder)
Pregnant women and women of child bearing capacity not accepting to use contraception for the duration of the study.
Individuals who have taken thalidomide within 3 months.
Anyone unwilling to return for follow-up.
IF ALL OF THE ABOVE ARE MET, LOOK AT THE NEXT SECTION TO ASSESS ELIGIBILITY FOR SPECIFIC STUDY

SPECIFIC ENTRY CRITERIA FOR EACH STUDY

Patients with Type 1 reaction

STUDY T1RA: New T1R

Individuals with clinical evidence of T1R with new nerve function impairment (NFI). A T1R is clinically defined by the acute development of erythema and oedema of skin lesions, often accompanied by neuritis and oedema of the hands, feet and face. New NFI is defined as less than 6 months duration of reduction in sensory, motor or autonomic function on history or examination.

OR

Individuals with new nerve function impairment without inflammation of skin lesions (if skin lesions are present)

STUDY T1RB: Recurrent T1R

Individuals with Type 1 Reactions who have not responded to at least 3 months of Prednisolone Treatment

Patients with ENL reaction

STUDY ENLA: New ENL

Individuals with clinical evidence of new ENL. New ENL is defined as the appearance of 6 or more tender, erythematous skin nodules for the first time in a patient with lepromatous or borderline lepromatous leprosy. In addition one or more of the following signs and symptoms may be present: fever (temperature >38°C), neuritis, joint pain, bone tenderness, oedema, malaise, anorexia and lymphadenitis.

STUDY ENLB: Recurrent ENL

Individuals with clinical evidence of chronic ENL. Recurrent or chronic ENL is defined by the presence of specific ENL symptoms in a patient with lepromatous or borderline lepromatous leprosy, who has had had ENL previously treated with prednisolone and has had a relapse or is still on prednisolone treatment but has poorly controlled ENL. The defining symptoms of ENL are 6 or more tender, erythematous skin nodules in conjunction with any of the following signs and symptoms: fever (temperature >38°C), neuritis, joint pain, bone tenderness, oedema, malaise, anorexia and lymphadenitis.

1. Informed consent

- Trial carefully explained by investigator or nurse.
- Patient given a choice whether or not to take part in trial.
- Written explanatory note available in Amharic and English (APPENDIX 1 and 2). Please give this to patient
- Individual's signature or mark obtained on consent form and PRF as proof of consent to take part in the trial.
- Signature of enrolling researcher.
- Keep a record of reasons why patients NOT recruited into study in the screening log book.
- Any patients refusing consent will be treated according to the standard protocol of the centre.
- Patients will not be offered incentive to consent to study

1. Registration

ONCE RECRUITED PATIENT WILL BE KNOWN ON ALL DOCUMENTATION BY A STUDY NUMBER.

The study number for each individual patient is made up of 10 letters or numbers.
To issue a study number:

1. Take STUDY CODE (4 letters: T1RA , T1RB, ENLA or ENLB) – describes which study the patient is in

2. NUMBER (3 digits) – patient recruitment sequence number in appropriate log book – there is a sequence for each study

3. PATIENTS INITIALS (3 letters: first name, second name, father's surname)

Study number: |__|__|__|__| |__|__|__| |__|__|__|

- RECORD DATE, NAME , CONTACT DETAILS, ALERT CLINIC NUMBER, STUDY NUMBER IN STUDY LOG BOOK – THERE IS A SEPARATE SECTION FOR EACH STUDY

- Write the study code of the study into which the patient has been recruited on the front of the patient's ALERT clinic notes.
- Provide patient with Study card with his own study number recorded on it.
- Ensure all the results are back, fill in a SF-36 QOL form
- Obtain a blank Patient Record Form and refer the patient to the physician with all the documentation.

LABORATORY INVESTIGATIONS

Study patient may have had most investigations prior to recruitment. Nurse to review all results and arrange any missing investigations. Please follow the following separate SOPs for:

- Specimen collection and transportation.
- Biopsy referral
- Biopsy procedure
- Laboratory
- Bacterial Index result second check

Laboratory tests

Full blood count (Hb and WBC total and differential)
Renal function (Serum creatinine, urea and electrolytes)
Liver Function Test
Random blood sugar - random blood sugar over 11mmol/l should be followed by a fasting glucose to rule out Diabetes Mellitus
Stool specimen will be examined for ova, cysts and parasites – if positive for strongyloidiasis or ameobiasis treatment will be started immediately, and a repeat stool examination will be performed after 2 and 4 weeks. This does not exclude patient.
Urinalysis – dipstick urine to rule out glucose and protein.
Pregnancy test for women of child-bearing age done on urine sample. The women will need counselling on the importance of contraception during the study period and referred to Family Planning Clinic.

HIV screening

All patients will be offered VCT by trained counsellor. The result will be discussed with patient with appropriate advice given. Record result.
HIV positive patients will be excluded from the Ciclosporin studies and will be referred to the ALERT HIV/ART department for further management.

TB screening

Consider TB screening (if long term cough, night sweats, weight loss- refer for Chest Radiograph and sputum AAFBs)

Skin Smear

- Skin smears from four sites including both ear lobes and two active skin lesions (the elbow or thigh should be used if there is only one skin lesion and both should be used if there are none). Smears are unnecessary if they have been done within 3 months of enrolment into the trial.

- All skin smear are stored in the lab for a period of one year minimum. When patients are recruited, please inform Lab Technician Tiruwork in order that she can review slides and confirm results

Biopsy

Skin Biopsies are taken by Sister Genet or Nurse Jemal in the biopsy room at AHRI.
Please refer patient with the appropriate pathology forms (3)
Punch biopsy of skin is taken for Ridley-Jopling classification and histopathology
6mm punch biopsy of skin at baseline. The site of biopsy should be clearly documented to enable subsequent biopsies to be taken from an adjacent site. Ulcerated lesions should be avoided if possible. USE PLAIN 1 0R 2% LIGNOCAINE DO NOT USE LIGNOCAINE WITH ADRENALINE.

Skin biopsy to be analysed by Dr Jemal Hussein of ALERT/ AHRI histology department.

Arrangements for sample referral

In case the ALERT Laboratory is unable to process certain samples (Potassium levels) arrangements have been made for referral to ICL (International Clinical Laboratories)

Please see SOP – ALERT LAB

Physiotherapy assessment

The study physiotherapists have been trained to do an accurate VMT /ST assessment. The results are recorded on a form designed specifically for the study. The form for the initial and final visit is slightly different as it contains a disability scoring section.
The physio assessment sheets will be stored serially with the PRF in order for the physician to assess nerve function progress. The investigators will then use the physio assessment sheet as the source document to fill in the clinical severity scale in the CRF.

Additional nerve tested for sensation but not included in the Clinical Severity Scale are (marked on diagram with □):

1. Radio-cutaneous nerve – sensation at thumb web on dorsal surface
2. Sural nerve – lateral border of the foot on dorsal surface
3. Common peroneal – big toe web on dorsal surface

Physiotherapy SOP

1. **Patient brought by runner for Physiotherapy VMT/ ST**
2. **Study Physiotherapist to use study form for VMT/ ST assessment**
3. **Voluntary motor testing (VMT)**

Facial, ulnar, radial, median and lateral popliteal nerves on each side are assessed and scored using the modified MRC grading for muscle power.
Facial nerve - Forced eye closure (orbicularis oculi)
Median nerve - Thumb abduction (abductor pollicis brevis)
Ulnar nerve - Little finger abduction (abductor digiti minimi)
Radial nerve - Wrist extension (extensor muscles)
Lateral popliteal nerve- Foot dorsiflexion (tibialis anterior, peroneus longus and brevis)
Posterior tibial nerve – Great toe grip (intrinsic muscles of foot). This is an additional test not included in severity score.

Testing procedure for each movement -The patient should be seated comfortably.

Facial nerve - Forced eye closure

- The patient is asked to close the eyes as tight as (s) he can.
- The tester tries to pull down the lower lid on both sides using his/her thumbs

Median nerve -Thumb abduction

- The wrist is held in extension and the patient is asked to lift his thumb up.
- Pressure is applied over the lateral side of the base of the proximal phalanx.

Ulnar nerve - Little finger abduction

- Ask the patient to abduct the little finger with MCP in slight flexion.
- Pressure is applied over the base of the proximal phalanx.

Radial nerve - Wrist extension

- Ask the patient to make a fist and lift the wrist up.
- Pressure is applied over the dorsum of hand.

Lateral popliteal nerve - Foot dorsiflexion

- Ask the patient to lift the foot up.
- Pressure is applied over the dorsum of foot.

Posterior tibial nerve – Great toe grip (intrinsic muscles of foot)

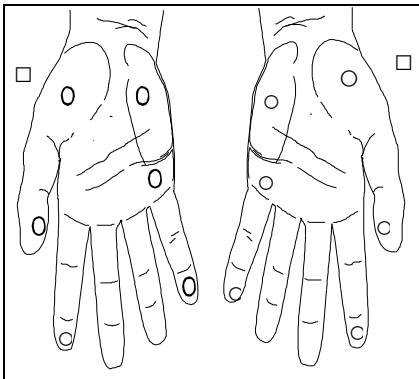
- Ask the patient to open up the space between the great toe and second toe.
- Pressure is applied the bases of the two toes

Score is derived for each nerve.

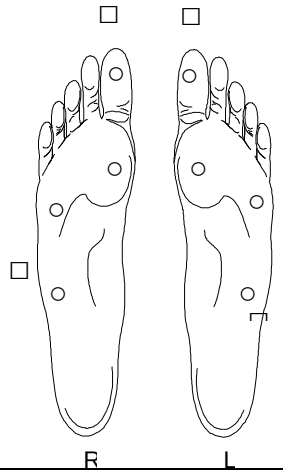
MRC modified grading of muscle power	
Score	Muscle response
5	Full range of movement (FROM)
4	FROM but less than normal resistance
3	FROM but no resistance
2	Partial range of movement with no resistance
1	Perceptible contraction of the muscle not resulting in joint movement
0	Complete paralysis

4. Sensory Testing

- Trigeminal*, ulnar, median and posterior tibial nerves on each side are tested with 5 filaments and recorded as follows



Mark the symbols clearly on the diagram above with appropriate filament number.
Begin with 0.2gm filament
○ Palmar aspect □ Dorsal aspect



Mark the symbols clearly on the diagram above with appropriate filament number.
Begin with 2gm
○ Plantar aspect □ Dorsal aspect

Perform the evaluation in the sequence listed below and document the first nylon with a positive response

Nylon colour	Approx force		
Blue	0.2gm	5	
Purple	2 gm	4	
Dark Red	4 gm	3	
Orange	10 gm	2	
Thick red	300 gm	1	
No response		0	
Unable to test	Mark 'U'	U	
Missing	Mark 'A'	A	

5. WHO disability grade done on the initial and final visits

WHO Grade	0	1	2
Eyes	Normal	-	Reduced vision (unable to count fingers at 6 metres). Lagophthalmos.
Hands	Normal	Loss of feeling in the palm of the hand	Visible damage to the hands, such as wounds, claw hands or loss of tissue.
Feet	Normal	Loss of feeling in the sole of the foot	Visible damage to the foot, such as wounds, loss of tissue or foot drop.

6. **During follow visits the physiotherapist will record any history of nerve function loss**
7. **Physiotherapist to sign and date the assessment sheet.**
8. **Send patient back to clinic with the assessment sheet**

CLINICAL SEVERITY SCALE for TYPE 1 REACTION

This will be recorded by the investigators in the Case Record Form by selecting the required information from the physiotherapy assessment sheets

Score A is related to skin lesion assessment done by the physician see physician examination section.

	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions	None	Erythema	Erythema and raised	Ulceration	
A2	Number of raised and/or inflamed lesions	0	1-5	6-10	>10	
A3	Peripheral oedema due to reaction	None	Minimal	Visible, but not affecting function	Oedema affecting function	
A SCORE						

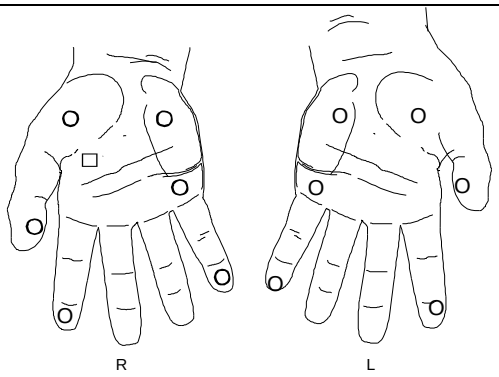
Score B: Sensory testing (ST)

- Trigeminal*, ulnar, median and posterior tibial nerves on each side. The Purple 2g and Orange 10g Semmes-Weinstein monofilaments are used at 3 sites for each nerve on the hand (median and ulnar). The Orange 10g and Pink 300g monofilament at 3 sites for the posterior tibial nerves. (* cotton wool is used)

- Record on the diagram of the hands and feet the result of the monofilament testing at each test site using the following symbols

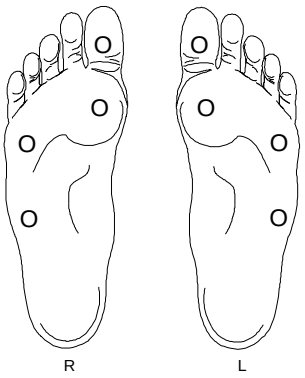
Purple 2g felt - ▲
Orange 10g felt - ■
Pink 300g felt - #
Neither monofilament felt – A
(Orange not felt on hands, Pink not felt on feet then mark an A at the site in question).

Sensory Assessment by Monofilament



Right Left

Mark the symbols clearly on the diagram above:
2g – Purple - ▲
10g – Orange - ■
Not felt at 10g - A
Missing/unable to test – Mark =U



Right Left

Mark the symbols clearly on the diagram above:
10g – Orange ■
300g – Pink #
Not felt at 300g - A
Missing/unable to test – Mark = U

	HANDS	Purple 2g Monofilament scores				Orange 10g Monofilament scores			Score
	Nerves	0	0.5	1	1.5	2	2.5	3	
B1	RIGHT Trigeminal	Felt						Not felt	
B2	LEFT Trigeminal	Felt						Not felt	
B3	RIGHT ulnar	All sites felt	1 site not	2 sites not	3 sites not	1 site not	2 sites not	3 sites not felt	
B4	LEFT ulnar	All sites felt	1 site not	2 sites not	3 sites not	1 site not	2 sites not	3 sites not felt	
B5	RIGHT median	All sites felt	1 site not	2 sites not	3 sites not	1 site not	2 sites not	3 sites not felt	
B6	LEFT median	All sites felt	1 site not	2 sites not	3 sites not	1 site not	2 sites not	3 sites not felt	
	FEET	Orange 10g Monofilament scores				Pink 300g Monofilament scores			Score
	Nerves	0	0.5	1	1.5	2	2.5	3	
B7	RIGHT posterior tibial	All sites felt	1 site not	2 sites not	3 sites not	1 site not	2 sites not	3 sites not felt	
B8	LEFT posterior tibial	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt	
B SCORE									

Score C: Voluntary motor testing (VMT)

i. Score is derived for each nerve.

MRC = 5 scores 0
MRC = 4 scores 1
MRC = 3 scores 2
MRC < 3 scores 3

If there is evidence of NFI for a given nerve then confirmation of the duration of the NFI should be sought from the affected individual to determine whether or not this is new.

Physiotherapist scores will be transferred into the severity scoring system.

	Nerve	0	1	2	3	Score
C1	RIGHT Facial	MRC =5	MRC= 4	MRC=3	MRC<3	
C2	LEFT Facial	MRC =5	MRC= 4	MRC=3	MRC<3	
C3	RIGHT Ulnar	MRC =5	MRC= 4	MRC=3	MRC<3	
C4	LEFT Ulnar	MRC =5	MRC= 4	MRC=3	MRC<3	
C5	RIGHT Median	MRC =5	MRC= 4	MRC=3	MRC<3	
C6	LEFT Median	MRC =5	MRC= 4	MRC=3	MRC<3	
C7	RIGHT Radial	MRC =5	MRC= 4	MRC=3	MRC<3	
C8	LEFT Radial	MRC =5	MRC= 4	MRC=3	MRC<3	
C9	RIGHT Lateral Popliteal	MRC =5	MRC= 4	MRC=3	MRC<3	
C10	LEFT Lateral Popliteal	MRC =5	MRC= 4	MRC=3	MRC<3	
TOTAL C SCORE						

MRC modified grading of muscle power		Severity Scale Score
Score	Muscle response	
5	Full range of movement (FROM)	0
4	FROM but less than normal resistance	1
3	FROM but no resistance	2
2	Partial range of movement with no resistance	3
1	Perceptible contraction of the muscle not resulting in joint movement	3
0	Complete paralysis	3

Total score will be worked out as follows:

Total score	Scores of A+B+C	

PHYSICIAN ASSESSMENT:

HISTORY AT REGISTRATION

The physician will fill the patient's medical history as per Patient Record Form.

- Patient details
- Leprosy classification and date of diagnosis
- Leprosy treatment (type, starting and completion dates(RFT))
- Time since completion of leprosy treatment
- Type of reaction
- Date of onset of reaction
- Symptoms of reaction (with particular attention to date of onset)
- Previous history of reactions and treatment received

Please use the following table to assist with Ridley Jopling classification:

Classification		Bacte-rial index	Skin lesions	Nerve involvement	Systemic features
Ridley- Jopling	WHO				
Indeterminate	PB	0	Solitary hypo-pigmented 2-5cm lesion. May become TT-like.	None clinically detectable.	Nil
Tuberculoid (TT)	PB/MB	0-1	Few, often one macule or plaque with well-defined border and sensory loss. The patch is dry (loss of sweating) and hairless.	May have one peripheral nerve enlarged. Occasionally presents as a mono-neuropathy.	Nil
Borderline tuberculoid (BT)	MB	0-2	Several larger irregular plaques with partially raised edges. Satellite lesions at the edges.	Asymmetrical multiple nerve involvement	Nil
Borderline (BB)	MB	2-3	Many macular lesions and infiltrated lesions with punched out centres.	Asymmetrical multiple nerve involvement	
Borderline lepromatous (BL)	MB	1-4	Many small macular lesions and multiple nodules and papules	Widespread nerve thickening. Sensory and motor loss.	
Lepromatous (LL)	MB	4-6	Numerous nodular skin lesions in a symmetrical distribution, not dry or anaesthetic. May present as many confluent macular lesions. There are often thickened shiny earlobes, loss of eyebrows and diffuse skin thickening.	Widespread nerve enlargement. Glove and stocking anaesthesia occurs late in disease.	Nasal stuffiness, epistaxis. Testicular atrophy. Ocular involvement. Bones and internal organs can be affected.

Record carefully every section of the medical history including the specific nerve function history.

EXAMINATION AT REGISTRATION

The physician will fill the patient's examination section as per Patient Record Form.

Clinical Examination includes:

- Full general clinical examination including T°, blood pressure and weight
- Leprosy clinical examination

  i. Nerves - signs and symptoms of neuritis
  (pain, tenderness, enlargement)

  ii. Skin - location of lesions (body chart)
  - type of lesions (patches, plaques, papules, nodules)
  - signs of inflammation in lesions
  - oedema of the hands and/or feet

Score A: Skin lesions and oedema

	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions	None	Erythema	Erythema and raised	Ulceration	
A2	Number of raised and/or inflamed lesions	0	1-5	6-10	>10	
A3	Peripheral oedema due to reaction	None	Minimal	Visible, but not affecting function	Oedema affecting function	
A SCORE						

A record is kept on the body chart of any skin lesions and oedema

The Physiotherapist VMT/ST result should be assessed at this point.

ENL severity will be recorded in the following form:

ENL Severity data collecting form

Symptoms of ENL

How many days have you been feeling unwell for (this episode of ENL): ____ days

How unwell do you feel now (tick one face)?

Have you noticed….	NO	YES
Any new lumps on your skin?		
Any new sensory loss?		
Any new weakness in your muscles?		
Any new tingling?		
Any new pain in your joints?		
Any new pain in your bones?		
Any new pain in your testicles?		
Painful eyes?		
Any visual disturbance?		

Examination

Number of ENL lesions (circle): 0 1-5 6-20 >20

Inflammation in the ENL lesions (circle): None
Erythema and pain – function not affected
Erythema and pain – function affected
Erythema and pain – function affected plus ulceration

(If patient has previous records use comparison to previous VMT/ST testing):

VMT:	MRC=5	MRC=4	MRC=3	MRC<3
ST decreased in:	None	One nerve	Two nerve	≥ three nerves
Nerve tenderness:	None	Tender on palpation	Withdraws	
Bone tenderness (shin):	None	Tender on palpation	Withdraws	
Oedema (ankle, face, hands):	None	Present	Gross	
Joint swelling:	None	Present	Affects function Which: _____	
Lymph nodes:	Normal	Enlarged and tender		
Testicles:	Normal	Tender (? Size)		
Temperature:	≤37.5°C	>37.5°C	level: _____	
Proteinuria (by dipstick):	Negative	Positive	level: _____	
Red eyes:	Yes	No	Ophthalmology	

Diagnosis:_____

The second study physician will assess the patient's reaction severity and review the patient's VMT/ ST results before making a comment here on page 10 of the PRF:

Second Physician comment:

PATIENT HAS:

TYPE 1 REACTION	□
ENL	□

Specialist opinion on the severity of today's Reaction:

Severe	□
Moderate	□
Mild	□

Comment and suggest normal therapy you would have prescribed:

……
……
……

This section will be used in the design of a severity scale

Results review

All results from the laboratory are entered in the result sheet of the PRF and reviewed. Any abnormal results will be noted and action taken if necessary by the physician.

Management of co-infection or other positive findings
After reviewing laboratory results and physical examination, the physician will ensure that the patient receives any necessary appropriate treatment as per normal standard ALERT management protocols. All treatment prescribed will be recorded in the PRF.

Final check:

The Physician will ensure that all the PRF section have been filled before referring the patient to Pharmacy for treatment allocation and dispensing.

Referral to pharmacy for treatment

The patient will be referred with a card that contains all the necessary information for the pharmacist:

Patient to Pharmacy card

Study number: |__|__|__|__||__|__|__||__|__|__|
Name: _____ Weight in kg: _____
Date Today: _____
Review date: _____
No of days Tx supplied: _____

The review date will have been worked out with the physician, according to review protocol. The Pharmacist will use the difference between the two dates to work out number of days treatment supplied.

PHARMACY

Please see the separate Pharmacy Standard Operating Procedures for further information
The following is a brief summary of what happens in the pharmacy.
The randomization process is described in the Principal Investigator's file.
The pharmacist has 4 boxes, one for each study, containing the envelopes with the randomized treatment allocation.
Once the patient arrives in the study pharmacy located in the Paeds unit, he will meet with the study pharmacist: Asegid Alem Tura.

The following process will be followed:

- The pharmacist will use the information on the patient card to fill patient pharmacy registration log.

- The pharmacist will select the packet for the correct study and the envelope with the corresponding sequence number as on the patient card. The envelope will be opened to reveal the treatment arm assignment.

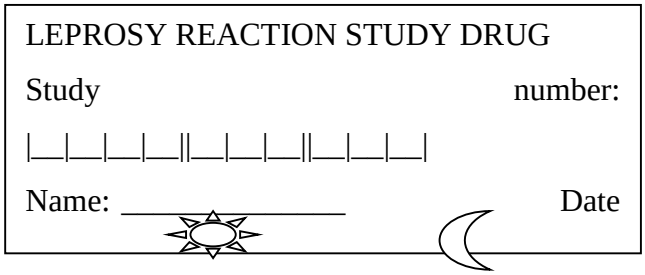
- The pharmacist will keep a confidential record the enrolment date, patient code and treatment arm assignment.

- Drug regimen sheets, (one for each treatment arm) in specified weight range have been pre-prepared and will serve as patient medication record sheet.

- Following the patient weight, the pharmacist takes out his previously prepared patient weight adjusted regimen sheet for the correct treatment arm. The patient's details will be recorded on this sheet.

- The treatment will be dispensed following the instruction on the above sheet carefully

- The drugs are collected after correct count in plastic envelopes with labels describing patient name, date, dose, duration, and date of expiry. Sample label is given below.



- The pharmacist will work out the number of days between the presenting date and the next review date in order to provide the patient with sufficient

amount of the drug. Number of days supplied will be marked on the patient card.

- Then the pharmacist will provide the patient with right amount of the drugs along with the right advice and carefully instruction.

- The pharmacist will record the patient's next review date in the patient treatment sheet as well as in the pharmacist diary or calendar in order to plan for follow up patient flow. The patient will be advised to return to the study physician after receipt of medication with the patient card.

- The study team will then record any changes in review date in the log book.

Patient card and Transport compensation.

Once the patient returns to the clinic, any new information will be recorded in the study log book. The patient will be provided with his own personal study card on which all the necessary information is recorded as well the phone number of his physician and the next appointment date.

Ciclosporin Study Patient card :

Name: _____

ALERT Hospital File number: _____

Study number: |__|__|__|__|: |__|__|__| : |__|__|__|

Present this card on arrival at RMC so your file can be prepared and you are seen by the correct physician

If you are unwell and attend the doctor outside ALERT Hospital, tell them you are on special treatment (immunosuppressive) and that they should contact the ALERT physician.

Physician's name: _____

Tel n°: _____

	Appointment date dd/mm/yyyy	Date seen dd/mm/yyyy	Extra notes
First visit			
Week 2			
Week 4			
Week 6			
Week 8			
Week 12			
Week 16			
Week 20			
Week 24			
Week 28			
Week 32			

The patient's transport costs will be compensated following the instruction on the patient travel SOP.

Quality of Life Questionnaire:

During the process of recruitment a Quality of Life Questionnaire: The SF-36 translated into Amharic will be complete with the help of a study nurse.

CHECKLIST AND PATIENT FLOW ON RECRUITMENT

Patient screened: Leprosy AND Reaction CONFIRMED. No exclusion criteria.
Patient informed re study, consent obtained

Study number issued: Enter patient in study log book and issue correct study number

Patient investigation: Nerve function: Physiotherapy worksheet

Laboratory:	VCT for HIV
	Bloods: FBC, Electrolytes, Creatinine, random glucose, LFT, ESR
	Skin smear
	Skin biopsy
	Stool: Microscopy
	Urine: dipstick and microscopy
	Urine: pregnancy test if woman in childbearing age
	Chest X-ray/ sputum if TB suspected
Quality of Life Questionnaire: to be done by study nurse	
Patient review by physician with results:	
	Fill in physician worksheet, ensuring all results available
Patient care:	Exclude if HIV positive – refer to ART clinic for standard ALERT management
	Exclude if suspected with TB
	If newly diagnosed leprosy patient: ensure registered in National register and started on MDT (WHO), refer to patient education, eye check and shoe room
	If woman of child bearing age: discuss contraception and refer to Health Centre or ALERT Gynaecology team
	If stool positive treat for ova and parasite, treat appropriately
	If urine positive for infection treat with antibiotics
Study action steps:	Refer patient to pharmacy with a study card
	Patient will be allocated into treatment arm
	Patient will receive treatment from pharmacist
	Patient returns to Physician with study card
Transport money:	Provide patient with review date and transport money

STORING SOURCE DOCUMENTS AND PRF

All the following source documents must be gathered and handed to the Study co-ordinator or PI:

Recruitment form

Consent Form

VMT/ST form

Laboratory results:
- Bloods
- Stool
- Urine
- BI
- Biopsy number
- Pregnancy test result

Any extra investigations dozen (eg Xray….)

Quality of Life Questionnaire

Patient to Pharmacy card

Completed PRF

All documentation will be reviewed by Study co-ordinator or by PI and stored in the metal cabinet in RMC under lock.

FOLLOW UP SCHEDULE

Patients will be reviewed according to a pre-specified schedule.

TABLE SUMMARISING TESTS DONE ON PATIENTS

	Base-line	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Tot
Clinical assessment	X	X	X	X	X	X	X	X	X	X	X	12
Renal function	X	X	X	X	X	X			X			7
FBC, LFT	X			X					X			3
Glucose (glucometer)	X	X	X	X	X	X	X	X	X	X		10
Stool (OCP) - PRN	X											1
Urinalysis - PRN	X											
HIV	X					X			X			2
Pregnancy test	X		X		X	X	X	X	X			7
TB screen	X											
Skin Biopsy	X						X					2

Clinical assessment will consist of:

- focussed questions to assess skin and nerve function and to detect adverse drug effects
- a general physical examination
- charting of skin lesions and nerve condition
- VMT ST assessment by physio
- weight
- Blood glucose and dipstick urinalysis for glucose and protein

Skin biopsy will be done at baseline for morphology and cytokines studies at baseline, week 16 and possibly at the end of the study.
HIV test will be repeated during the study period if clinically indicated by symptoms or worsening health status. It will be done also at the end of the study.

Summary of treatment regimens

Study 1: Cn and prednisolone in Type 1 Reactions

		ARM 1		ARM 2		
		PREDNISOLONE		CICLOSPORIN		PREDNISOLONE
		Prednisolone		Ciclosporin	AND	Predn
Clinical R.	Day 0					
	Week 1	40mg		7.5mg/kg		40mg
Clinical R.	Week 2	40mg		7.5mg/kg		40mg
	Week 3	35mg		7.5mg/kg		20mg
Clinical R.	Week 4	35mg		7.5mg/kg		10mg
	Week 5	30mg		7.5mg/kg		
Clinical R.	Week 6	30mg		7.5mg/kg		
	Week 7	25mg		7.5mg/kg		
Clinical R.	Week 8	25mg		7.5mg/kg		
	Week 9	20mg		7.5mg/kg		
	Week 10	20mg		7.5mg/kg		
	Week 11	20mg		7.5mg/kg		
Clinical R.	Week 12	20mg		7.5mg/kg		
	Week 13	15mg		6mg/kg		
	Week 14	15mg		6mg/kg		
	Week 15	15mg		6mg/kg		
Clinical R.	Week 16	15mg		6mg/kg		
	Week 17	10mg		4mg/kg		
	Week 18	10mg		4mg/kg		
	Week 19	5mg		2mg/kg		
Clinical R.	Week 20	5mg		2mg/kg		
	Week 21	n/a		n/a		
	Week 22	n/a		n/a		
	Week 23	n/a		n/a		
Clinical R.	Week 24	n/a		n/a		
Clinical R.	Week 28	n/a		n/a		
Clinical R.	Week 32	n/a		n/a		

Placebo not marked on above table for simplification

Study 2: Cn and Prednisolone in ENL Management

		ARM 1		ARM 2		
		PREDNISOLONE		CICLOSPORIN		PREDNISOLONE
		Prednisolone		Ciclosporin	AND	Predn
Clinical R.	Day 0					
	Week 1	60mg		7.5mg/kg		40mg
Clinical R.	Week 2	55mg		7.5mg/kg		40mg
	Week 3	50mg		7.5mg/kg		20mg
Clinical R.	Week 4	45mg		7.5mg/kg		10mg
	Week 5	40mg		7.5mg/kg		
Clinical R.	Week 6	35mg		7.5mg/kg		
	Week 7	30mg		7.5mg/kg		
Clinical R.	Week 8	25mg		7.5mg/kg		
	Week 9	20mg		7.5mg/kg		
	Week 10	20mg		7.5mg/kg		
	Week 11	15mg		7.5mg/kg		
Clinical R.	Week 12	15mg		7.5mg/kg		
Clinical R.	Week 13	10mg		6mg/kg		
	Week 14	10mg		6mg/kg		
Clinical R.	Week 15	5mg		4mg/kg		
	Week 16	5mg		2mg/kg		
	Week 17	n/a		n/a		
	Week 18	n/a		n/a		
	Week 19	n/a		n/a		
Clinical R.	Week 20	n/a		n/a		
Clinical R.	Week 24	n/a		n/a		
Clinical R.	Week 28	n/a		n/a		
Clinical R.	Week 32	n/a		n/a		

Placebo not marked on above table for simplification

FOLLOW UP ACTIVITIES

1. Welcoming patient

Study participants will all carry a card with name, study number and list of a review dates. This will be presented at the clinic on arrival so as to direct the patient correctly through the process of that review.

2. Checking register and marking visit

Nurse or runner receiving patient will check in log file for the patient's details, confirm details with patient and obtain the PRF

3. Obtaining PRF and organising planned investigations

All PRF are kept in the locked metal cupboard in Red Medical Clinic. Obtain the correct PRF, confirm the follow up week number and organise list of investigations for that specific week. Fill in request forms for the laboratory

4. Nurse's review: weight BP pulse

The nurse will obtain the following vital statistics and attach to patient's record: Temperature, pulse, Blood pressure and weight

5. Laboratory sample collected

Depending on the week number, the sample collecting and tracking forms are filled in and the corresponding specimens collected as per standard. Specimens are sent to lab as soon as possible (see Laboratory SOP)

6. Physiotherapy assessment

The patient is then sent to Physiotherapy for VMT and ST assessment with the appropriate for, attention of study physiotherapists

7. Physician's history and examination

Once results are collected, the nurse will check that all necessary documentation is attached to the PRF and refer the patient to the study physician. After the physician's assessment and management of any complications the patient is given a "Clinic to Pharmacy card" with today's weight and the next review appointment

8. Referral to Pharmacy

The study pharmacist will receive the patient with the card above and proceed to identify the patient and obtain his treatment card.
Any weight adjustment will be taken note of. The patient will then be issued with the treatment drugs and instructions on how to take these. See Pharmacy SOP

9. Appointment date registered

The pharmacist will approve the review date and mark the number of days treatment was supplied for on the patient card, before referring patient back to clinic

10. Transport allowance provided

The patient's appointment date will be record in the clinic diary and he will be provide with the transport cost as per travel SOP.

11. All results gathered and attached to PRF
Physician will ensure that all source documents are attached to the PRF

12.PRF storage

Study Physician or co-ordinator will ensure that completed documents are stored in the locked metal cabinet

- **CHECKLIST ON REVIEW**

History
Physical examination
Nerve studies by physiotherapy department
Skin smears if not done in previous 3 months
Skin biopsy from the edge of an area of reactional (non-ulcerated) skin –only week 6, 16 and 32

Blood test: FBC, renal function, random glucose
Stool sample, Urine sample
Chest Xray and Sputum if suspicion of TB

Encourage appropriate contraception in females with childbearing capacity

Refer to pharmacy to collect further treatment
Review date arranged. Transport provided

USING ADDITIONAL PREDNISOLONE

When additional Prednisolone is required, the standard pink tablets will be prescribed.

- Criteria for using additional prednisolone
  - i. Sustained deterioration for a period of at least two weeks of:
    - a. Deterioration in nerve function
    - b. Nerve pain unresponsive to analgesics
    - c. Palpable swelling of skin patches
    - d. New erythematous and raised skin patches
  - ii. Deterioration in nerve function which the study doctors believe requires immediate additional Prednisolone

- The patient must be examined by at least two of the study doctors and they should be in agreement about giving the patient additional Prednisolone.
- The reasons for the additional Prednisolone and the date started should be recorded.

Regimen for additional prednisolone

- If there is recurrence of T1R with NFI (or nerve pain unresponsive to analgesics) on treatment then add extra Prednisolone to make up a total of 40mg when the present dose of Prednisolone is known, and then taper according to the original regimen.

- In cases belonging to Study 1A, where the study is blinded and the clinician is unable to know whether the patient is on Prednisolone or Ciclosporin, then add Prednisolone 20mg and taper down.

- If there is recurrence of T1R with skin signs but no NFI then:

    i. If recurrence within the first ten weeks of treatment or there is facial involvement then add extra Prednisolone to make up a total of 40mg and then taper according to the original regimen.
    ii. If recurrence after ten weeks of treatment then add extra Prednisolone to make up a total of 20mg and then taper according to the original regimen.

Adverse events

Managing Adverse Events

At each clinical review during the study period the patient will be closely monitored for any signs of adverse effects related to the study drugs, but also unrelated adverse events will be recorded as will the causality be assessed.

Adverse events will usually be picked up in the careful history taking and general examination, but specific known drug related adverse event are listed in Table below and the physician should enquire about each one specifically.

Symptoms or signs to monitor	
Moon face	□
Acne	□
Gum hyperplasia	□
Cutaneous (including nails) fungal infections	□
Gastric pain requiring antacid	□
Gastrointestinal bleeding	□
Nocturia, polyuria, polydipsia	□
Diabetes mellitus	□
Psychosis or other mental health problems	□
Weight loss >5kg	□
Weight gain	□
Glaucoma	□
Cataract	□
Hypertension BP > 160/90 on 2 separate readings at least 1/52 apart	□
Infections	□
Infected ulcers	□
Corneal ulcer	□
Tuberculosis	□
Night sweats	□
Convulsions	□
Vomiting	□
Diarrhoea	□
Breathing difficulties	□
Abnormal blood results (hyperkalaemia, abnormal LFT)	□
Pruritus	□

A list of common medication related side effects is attached here to help the physician identify the potential causal factor and plan appropriate management of the patient:

Prednisolone side effects:

- Major adverse events
    i. Gastrointestinal bleeding
    ii. Nocturia, polyuria, polydipsia

iii. Diabetes mellitus
iv. Psychosis or other mental health problems
v. Weight loss >5kg
vi. Weight gain
vii. Glaucoma
viii. Cataract
ix. Hypertension >160/90 on two separate readings at least one week apart
x. Infections
xi. Infected ulcers
xii. Corneal ulcer
xiii. Tuberculosis
xiv. Night sweats

- Minor adverse events
  i. Moon face
  ii. Acne
  iii. Cutaneous (including nails)fungal infections
  iv. Gastric pain requiring antacids

Ciclosporin side effects:

i. Hypertension
ii. Nausea, vomiting, diarrhoea
iii. Weakness, fatigue, weightloss, headache
iv. Renal impairment
v. Hypertrichosis
vi. Gingival overgrowth

Contra-indications to Ciclosporin:

i. Abnormal renal function
ii. Uncontrolled hypertension
iii. Breastfeeding (Ciclosporin passed into breast milk)
iv. Acute severe infections (including active TB)

Drug interactions with Ciclosporin:

i. Agents that increase Ciclosporin levels:

Erythromycin	Ketoconazole	Allopurinol
Doxycycline	Cimetidine	Oral contraceptives
Clarithromycin	Metoclopramide	Grapefruit juice
Norfloxacin	Verapamil	
Chloroquine	Diltiazen	

ii. Agents that decrease Ciclosporin levels:

Rifampicin	Phenythoin	Carbamazepine
Trimethoprim (IV)	Phenobarbitone	

iii. Agents that increase nephrotoxicity:

NSAIDS (care with high doses)	Co-trimoxazole
Aminoglycosides	Trimethoprim

iv. Ciclosporin increases the plasma concentration of prednisolone.

Important laboratory monitoring:

1. Serum Creatinine:
   If level increases more than 30% above baseline, on more than 1 measurement, then dose of ciclosporin should be reduced by 1mg/kg
   If level increases more than 50% above baseline, reduce dose of ciclosporin by 50%
2. Serum Potassium
   If serum Potassium ranges 5.0 – 6.4mmol/l, reduce ciclosporin dose by 1mg/kg. Repeat Potassium after 2 days. If still in this range then reduce dose by 1mg/kg and repeat blood test every 2 days until within normal level.
   If serum Potassium >6.4 mmol/l, STOP ciclosporin. Five 50ml of 50% IV dextrose plus 5 units of Actrapid over 20 minutes followed by 1 litre 10% dextrose IV given over 12 hours. Repeat serum Potassium the following day and every 2 days after until within the normal range.

Managing clinical symptoms:

Clinical Parameter	**Level**	**Action**
Blood Pressure	If BP> 100mg diastolic after maximal antihypertensive therapy	Stop Cn
	If BP moderately elevated	Reduce ciclosporin by 25% or introduce anti-hypertensive (avoid K+ sparing agent – may cause hyperkalaemia)
Gingival overgrowth	Severe	Reduce Cn by 1mg/kg
Hypertrichosis	Noticeable but not unacceptable to patient	Reassure and continue Cn
Hypertrichosis	Unacceptable to patient	Stop Cn
Nausea and vomiting	Mild, treatable	Anti-emetics
Nausea and vomiting	Severe	IV rehydration STOP Cn
Diarrhoea	Severe (every hour and leading to dehydration)	Stop Cn and restart dose reduced by 1mg/kg after dehydration resolved
Malaise		Measure Potassium
Gastric pain		Antacids/ Ranitidine

All adverse events will be recorded in the Patient Record Form and Case Record Form.

Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to the IMP qualify as adverse reactions.

Serious Adverse Event/ Reaction (SAE/SAR)

Any adverse event or adverse reaction that at any dose:

- results in death
- is life-threatening

- requires hospitalisation, or prolongation of existing inpatients' hospitalisation.
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Serious Adverse Reaction (SSAR)

Any adverse reaction that is classed as serious and which is consistent with the information about the IMP listed in the Summary of Product Characteristics.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse reaction that is classed as serious and is suspected to be caused by the IMP that is not consistent with the information about the IMP in the Summary of Product Characteristics, i.e. it is suspected and unexpected.

Severity and causality will be commented upon by the study physician in the CRF.

Serious Adverse Events

A reporting form has been prepared for Serious Adverse Events.
These will be immediately reported to the DSMB by the study physician and/or the PI.

Admission

Patients may be admitted for the first day (Day0) to have all initials tests done and results back prior to starting study, if this is more convenient for patient.
Patients will generally be treated as out-patients, but may be offered admission at ALERT if unwell.

Criteria for hospitalization:

1. Patient is to unwell to be at home
2. Patient develops severe infection
3. Patient develops severe nausea, vomiting and /or diarrhoea requiring i.v. re hydration
4. Patient has abnormal blood results with potassium > 6.4 mmol or serum creatinine increased by 30% above baseline
5. Patient is unable to travel between home and hospital, e.g. foot ulcer requiring bed rest; lives too far and is willing/ prefers admission.

Arrangements for breaking the code in the event of an agreed clinical emergency.

- In the event of a major adverse event necessitating hospital admission then the code can be broken for that individual in order to aid management of the problem.
- Two study physicians will agree on the necessity to break the code.
- The pharmacist will be informed and provide details of treatment allocation.
- The patient will be withdrawn from the study.
- A Serious Adverse Event Form will be completed.
- The DSMB will be informed of this event.

Late Clinic Attendances

If a trial subject does not attend a scheduled assessment then they will be contacted and asked to come as soon as possible for their assessment. It is essential that the date of the attendance is recorded. The number of the assessment should not be changed regardless of how late the assessment is carried out.

The next assessment after this should be scheduled as though the original assessment had been performed as planned. If the assessment is so late that the following assessment has also been missed then the next assessment should be scheduled for 28 days (four weeks) later.

If a participant has missed certain trial investigations then these should be performed when they next attend.

Unscheduled Clinic Attendances/examinations

- All unscheduled examinations (if an inpatient) or clinic attendances should be recorded on Form 7: Unscheduled visit
- It should be documented if the clinician feels the attendance is related to prednisolone or ciclosporin therapy.

Data management

- Each subject enrolled into the study will have two individual case booklets for recording of all clinical and laboratory data:

    1. Patient Record Form: all forms needed for patient management, including physician and physiotherapist worksheets and source documents (eg lab results…). This will be used in clinic to record all information during patient attendance.
    2. Case Record Form: this is the data record which is essential for study data. It will be filled in daily by the study physician following patient attendance. This will be stored separately in a secured place and only accessible to named study physicians.

- An anonymised Access database will be created for storage of trial data which will subsequently be analysed using standard statistical packages.

- Double entry of data into database will be done. One entry to be done by PI and second entry by data management staff at ALERT/AHRI. The two entries will be crossed checked for errors using EPI-INFO, and any differences verified by going back to original data on CRF.

- Data analysis will be done using SPSS.

- PRF and CRF will be stored at the end of the study in the secure archiving area at AHRI and remain the property of ALERT/AHRI.

APPENDIX 13: PATIENT RECORD FORM

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Patient Record Form

For

Ciclosporin in the management of Leprosy Reactions
Based at ALERT Hospital

PHYSICIAN TO CHECK CORRECT ALLOCATION OF STUDY NUMBER

Please tick relevant study

Study 1A: new Type 1 Reactions in Leprosy ☐

Study 1B: steroid resistant Type 1 Reactions in Leprosy ☐

Study 2A: new Erythema Nodosum Leprosum ☐

Study 2B: chronic or recurrent Erythema Nodosum Leprosum ☐

Investigators:

Dr Saba Lambert,
Prof Diana Lockwood,
Dr Elizabeth Bizuneh
Dr Shimeles Nigusse Doni
Dr Digafe Tsegaye
Dr Jamal Hussein – Pathology
Dr Lawrence Yamuah – Data management

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

ASSESSMENT RECORD

Start Date: (dd/mm/yyyy) __ __ / __ __ / __ __ __ __

	Date due dd/mm/yyyy	Date done dd/mm/yyyy	Extra notes
Base line			
Week 2			
Week 4			
Week 6			
Week 8			
Week 12			
Week 16			
Week 20			
Week 24			
Week 28			
Week 32			
Unscheduled review			
Unscheduled review			
Adverse Events			
Study Termination			

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

PHYSICIAN WORKSHEET AT REGISTRATION **Baseline – Day 0**

Leprosy History

Study Patient Number: |__|__|__|__||__|__|__||__|__|__|	**Hospital File number:** _____ **Leprosy Registration number:** _____
Assessed by: ***Name***	**Today's Date:** __/__/____ ***dd/mm/yyyy***
Patient Initial: |__|__|__|	**Home village / town**
Sex: ***M*** |__| ***F*** |__|	**Age *(Yrs)*:** |__|__|
Date of leprosy diagnosis: __/__/____	**Classification (Ridley- Jopling):** **Clinically** **1. TT** |__| **2. BT** |__| **3. BB** |__| **4. BL** |__| **5. LL** |__| **Histology** **1. TT** |__| **2. BT** |__| **3. BB** |__| **4. BL** |__| **5. LL** |__|
Duration of leprosy (*number of months since first sign)* |__|__|__|	**Classification of leprosy (WHO):** **1. PB** |__| **2. MB** |__|
Bacterial Index at time of diagnosis: |__|__|__|__|__|__| **Date:** __/__/____	**Most recent Bacterial Index:** |__|__|__|__|__|__| **Date:** __/__/____
MDT Start Date: __/__/____ **MDT Stop Date:** __/__/____ **(RFT)**	**Previous Treatment Default?** **1. Yes** |__| **2. No** |__|

Is this a presentation of a new Reaction? **1. Yes** |__| **2. No** |__| **What type of reaction is it: T1R** **(circle) ENL**	**Date of onset of Leprosy Reaction** __/__/____ **Duration of Reaction symptoms on this occasion (in days /weeks):**
Previous history of reactions: **1. Yes** |__| **2. No** |__| Details (how many?):	**Time since last reaction (in months)** if first reaction then record X _____

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

General Medical History

	1. Yes	2.No
Any major medical diagnoses?	☐	☐

If yes, specify:

1. Diabetes |__|
2. Hypertension |__|
3. Tuberculosis |__|
4. Other |__|

_____

Other Medical History

Diagnosis	Date of onset	Date of resolution *
1.	/ /	/ /
2.	/ /	/ /
3.	/ /	/ /

Known allergies: _____

_____

Current medications (other than MDT and including analgesia)

Drug and reason starting	Date started dd/mm/yyyy	Ongoing treatment Yes or No
1.	/ /	
2.	/ /	
3.	/ /	

PREDNISOLONE HISTORY:
If the patient has taken prednisolone in the past please describe in detail dosage and period:

_____ _____

_____ _____

_____ _____

_____ _____

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Baseline symptoms questionnaire.

Symptoms related to:	
Moon face	☐
Acne	☐
Gum hyperplasia	☐
Cutaneous (including nails) fungal infections	☐
Gastric pain requiring antacid	☐
Gastrointestinal bleeding	☐
Nocturia, polyuria, polydipsia	☐
Diabetes mellitus	☐
Psychosis or other mental health problems	☐
Weight loss >5kg	☐
Weight gain	☐
Glaucoma	☐
Cataract	☐
Hypertension BP > 160/90 on 2 separate readings at least 1/52 apart	☐
Infections	☐
Infected ulcers	☐
Corneal ulcer	☐
Tuberculosis	☐
Night sweats	☐
Convulsions	☐
Vomiting	☐
Diarrhoea	☐
Breathing difficulties	☐
Abnormal blood results (hyperkalaemia, abnormal LFT)	☐
Pruritus	☐

	1. Yes	2.No
Consider TB screening (if long term cough, night sweats, weight loss- refer for CXR and sputum AFBs)	☐	☐

Describe events: _____
_____
_____
_____

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Nerve function History

Ask the patient if s/he has experienced any of the following symptoms in the last 6 months:

Patient's report of new symptoms since last assessment									
	RIGHT				*LEFT*				
	ELBOW	*HAND*	*KNEE*	*FOOT*	*ELBOW*	*HAND*	*KNEE*	*FOOT*	*OTHER*
Diminished sensation – **eg unable to feel hot or cold, numbness (Y/N)**									
New Weakness **(Y/N)**									
Paraesthesia - **eg pins and needles, insects crawling (Y/N)**									
Nerve Pain **eg burning sensation, shooting pain (Y/N)**									

Patient's report of skin lesions in the last 6 months:

When did they notice the first patch?				
When did the skin patches become inflammed?				
Have they developed new skin patches recently? (Y/N)				
How many new skin patches have developed recently?				
Do you feel your skin is worse, the same or better?				
Facial patch? (Y/N)				
Facial patch inflammation. (Circle)	**NONE**	**ERYTHEMA**	**ERYTHEMA AND RAISED**	**ULCERATED**

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

EXAMINATION AT REGISTRATION - PHYSICIAN

Baseline Physical Examination – Month 0

Date: (dd/mm/yyyy) __ __ / __ __ / __ __ __ __

I. Vital signs

Temp	Pulse	B.P. (systolic/ diastolic)
|__|__|.|__|	|__|__|__|	|__|__|__| / |__|__|__|

II. Weight: |__|__|__|.|__|kg

III. General examination

	1.Normal	2.Abnormal	3.Not examined	If abnormal specify
Head and neck				
Lymph nodes				
Skin (non leprosy)				
Lungs				
Heart				
Abdomen				
Liver				
Spleen				
Ext Genitalia (male)				

IV. Leprosy Examination

i. Nerves - signs and symptoms of neuritis (new = less than 6 months)

Name of nerve	Nerve tenderness - Grade*	Nerve enlargement (yes or no)	Motor symptoms – weakness (√ if yes)		Sensory symptoms – numbness, pain(√ if yes)	
			Old	New	Old	New
R Cervical/GA, Facial					N/A	N/A
L Cervical/ GA, Facial						
R Ulnar						
L Ulnar						
R Median						
L Median						
R Radial/ R.C.					N/A	N/A
L Radial/ R.C.					N/A	N/A
R lat popliteal						
L lat popliteal						
R Post Tibial						
L Post Tibial						

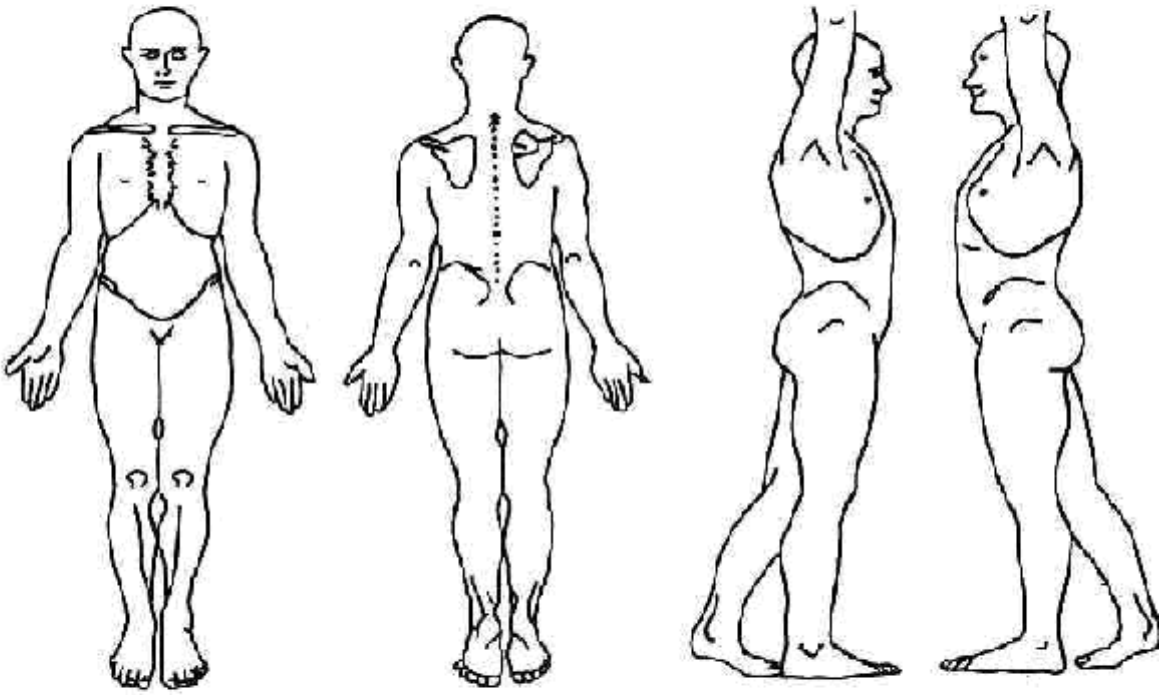
* Grading for nerve tenderness: 0=none 1= mild tenderness
2= withdrawal/ wincing 3= not allowing palpation

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

EXAMINATION AT REGISTRATION **Baseline – Day 0**

ii. Skin
- location of lesions (body chart)
- type of lesions (patches, plaques, papules, nodules)
- signs of inflammation in lesions
- oedema of the hands and/or feet
- mark skin biopsy site, Date: __/__/____

Body Chart



	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions	None	Erythema	Erythema and raised	Ulceration	
A2	Number of raised and/or inflamed lesions	0	1-5	6-10	>10	
A3	Peripheral oedema due to reaction	None	Minimal	Visible, but not affecting function	Oedema affecting function	
A SCORE						

  PRF completed by: _____ Date: _____ 8/111

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

IF PATIENT HAS ENL–PHYSICIAN TO COMPLETE THE FOLLOWING ENL DATA COLLECTING FORM **Baseline – Day 0**

Symptoms of ENL

How many days have you been feeling unwell for (this episode of ENL): ____ days

How unwell do you feel now (tick one face)?

Have you noticed….	NO	YES
Any new lumps on your skin?		
Any new sensory loss?		
Any new weakness in your muscles?		
Any new tingling?		
Any new pain in your joints?		
Any new pain in your bones?		
Any new pain in your testicles?		
Painful eyes?		
Any visual disturbance?		

Examination

Number of ENL lesions (circle): 0 1-5 6-20 >20

Inflammation in the ENL lesions (circle):
None
Erythema and pain – function not affected
Erythema and pain – function affected
Erythema and pain – function affected plus ulceration

(If patient has previous records use comparison to previous VMT/ST testing):

VMT:	MRC=5	MRC=4	MRC=3	MRC<3
ST decreased in:	None	One nerve	Two nerve	≥ three nerves
Nerve tenderness:	None	Tender on palpation		Withdraws
Bone tenderness (shin):	None	Tender on palpation		Withdraws
Oedema (ankle, face, hands):	None	Present		Gross
Joint swelling:	None	Present		Affects function Which: _____
Lymph nodes:	Normal	Enlarged and tender		
Testicles:	Normal	Tender (? Size)		
Temperature:	≤37.5°C	>37.5°C		level: _____
Proteinuria (by dipstick):	Negative	Positive		level: _____
Red eyes:	Yes	No		Ophthalmology diagnosis:_____

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

CONFIRM YOU HAVE SEEN AND ATTACHED VMT/ST FORM ☐

Second Physician comment:

PATIENT HAS :

TYPE 1 REACTION ☐

ENL ☐

Specialist opinion on the severity of today's Reaction:

Severe ☐

Moderate ☐

Mild ☐

Comment and suggest normal therapy you would have prescribed:

.....

.....

.....

.....

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

INVESTIGATIONS – Physician to Complete **Baseline – Day 0**

Laboratory tests **(record results)**

	Date taken dd/mm/yyyy	Result
FBC	--/--/----	Hb: |__|__|.|__| g/dl WCC: |__|__|__|__| Plt:					ESR			
Renal function	--/--/----	Creat: |__|__|.|__|__| mg/dl Urea |__|__|.|__| mg/dl K+: |__|__|.|__| meq/l Na: |__|__|.|__| meq/l Glucose |__|__|__| mg/dl
LFT	--/--/----	Alk phos |__|__|__| iu/l ASAT |__|__|__| iu/l ALAT |__|__|__| iu/l Bilirubin total |__|__|__| mg/dl
HIV Rapid test (via VCT)	--/--/----	1. Positive |__| 2. Negative |__|
Blood sugar (glucometer)	--/--/----	|__|__|
Stool for ova, cysts and parasites	--/--/----	1. Positive	__	 2. Negative		
Urinalysis (dipstick)	--/--/----	1. Positive |__| 2. Negative |__| Specify: _____
Pregnancy test (urine)	--/--/----	1. Positive |__| 2. Negative |__| Advise re contraception options

Skin Smear and Biopsy

1. Confirm skin smear already done at diagnosis ☐
2. Skin Biopsy taken from a typical skin lesion for Ridley- Jopling classification and histology.

AHRI number -_____

Date done (dd/mm/yyyy): _ _ / _ _ /_ _ _ _ Site of biopsy: _____

***EXTRA MEDICATION PRESCRIBED TODAY*:**

_____

_____

_____

COMPLETE PHARMACY CARD AND SEND PATIENT TO PHARMACY

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

PHYSICIAN WORK SHEET: FOLLOW-UP

AT EACH REVIEW AND UNPLANNED VISIT, COMPLETE:

Insert the relevant week number: **Week** |__|__|

And date: **Date:** _ _ / _ _ / _ _ _ _

Physician to complete history and examination and ensure lab results are entered

Physician to complete adverse event form if necessary

Ensure correct physiotherapy form is attached to PRF

After each visit:

1. **mark off visit on page 2: Assessment Record**
2. **Write in date of next planned visit on page 2: Assessment Record**
3. **Tell Investigator about completed patient review in order to transfer data to CRF**

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__|
Date: __ / __ / ____

Ask patient about new symptoms since last review:
Did you notice any new loss or sensation in your hands or feet?
Did you notice any new dryness of your hands palms or foot soles?
Did you notice any new weakness in your hand or feet?
Did you notice any new sensation of pins and needles in your hands or feet?
Did you notice any new pain sensations (burning/ shooting)?
New additional medications (other than MDT and including analgaesia)

Ask the patient if s/he has experienced any of the following symptoms since the last assessment:

Patient's report of new symptoms since last assessment									
	RIGHT				*LEFT*				
	ELBOW	*HAND*	*KNEE*	*FOOT*	*ELBOW*	*HAND*	*KNEE*	*FOOT*	*OTHER*
Diminished sensation – eg unable to feel hot or cold, numbness (Y/N)									
New Weakness (Y/N)									
Paraesthesia - eg pins and needles, insects crawling (Y/N)									
Nerve Pain eg burning sensation, shooting pain (Y/N)									

Patient's report of skin lesions since last assessment

Have the inflamed skin patches improved? (Y/N/STABLE)				
How many skin patches have improved since last visit?				
Have they developed new skin patches recently? (Y/N)				
How many new skin patches have developed recently?				
Do you feel your skin is worse, the same or better?				
Facial patch? (Y/N)				
Facial patch inflammation. (Circle)	NONE	ERYTHEMA	ERYTHEMA AND RAISED	ULCERATED

 PRF completed by: _____ Date: _____ 13/111

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__| **Date:** __/__/____

New medications:

Drug and reason starting	Date started dd/mm/yyyy	Ongoing treatment Yes or No
1.	/ /	
2.	/ /	
3.	/ /	

Symptoms questionnaire. ***Has the patient had any problems with the reaction treatment or any of the following symptoms or conditions diagnosed since starting the reaction treatment?***

Symptoms related to:	
Moon face	☐
Acne	☐
Gum hyperplasia	☐
Cutaneous (including nails) fungal infections	☐
Gastric pain requiring antacid	☐
Gastrointestinal bleeding	☐
Nocturia, polyuria, polydipsia	☐
Diabetes mellitus	☐
Psychosis or other mental health problems	☐
Weight loss >5kg	☐
Weight gain	☐
Glaucoma	☐
Cataract	☐
Hypertension BP > 160/90 on 2 separate readings at least 1/52 apart	☐
Infections	☐
Infected ulcers	☐
Corneal ulcer	☐
Tuberculosis	☐
Night sweats	☐
Convulsions	☐
Vomiting	☐
Diarrhoea	☐
Breathing difficulties	☐
Abnormal blood results (hyperkalaemia, abnormal LFT)	☐
Pruritus	☐

Any other relevant new history:

_____

_____

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__| **Date:** __/__/____

FOLLOW UP EXAMINATION -

I. Weight: |__|__|__|.|__|**kg**

II. Vital signs

Temp	Pulse	B.P. (systolic/ diastolic)
|__|__|.|__|	|__|__|__|	|__|__|__|/|__|__|__|

III. General examination

	1.Normal	2.Abnormal	3.Not examined	If abnormal specify
Head and neck				
Lymph nodes				
Skin (non leprosy)				
Lungs				
Heart				
Abdomen				
Liver				
Spleen				
Ext Genitalia (male)				

IV. Leprosy Examination

i. Nerves - signs and symptoms of neuritis (since last review)

Name of nerve	Nerve tenderness - Grade*	Nerve enlargement (yes or no)	Motor symptoms – weakness (√ if yes)		Sensory symptoms – numbness, pain(√ if yes)	
			Old	New	Old	New
R Cervical/GA, Facial					N/A	N/A
L Cervical/ GA, Facial						
R Ulnar						
L Ulnar						
R Median						
L Median						
R Radial/ R.C.					N/A	N/A
L Radial/ R.C.					N/A	N/A
R lat popliteal						
L lat popliteal						
R Post Tibial						
L Post Tibial						

* Grading for nerve tenderness: 0=none 1= mild tenderness
2= withdrawal/ wincing 3= not allowing palpation

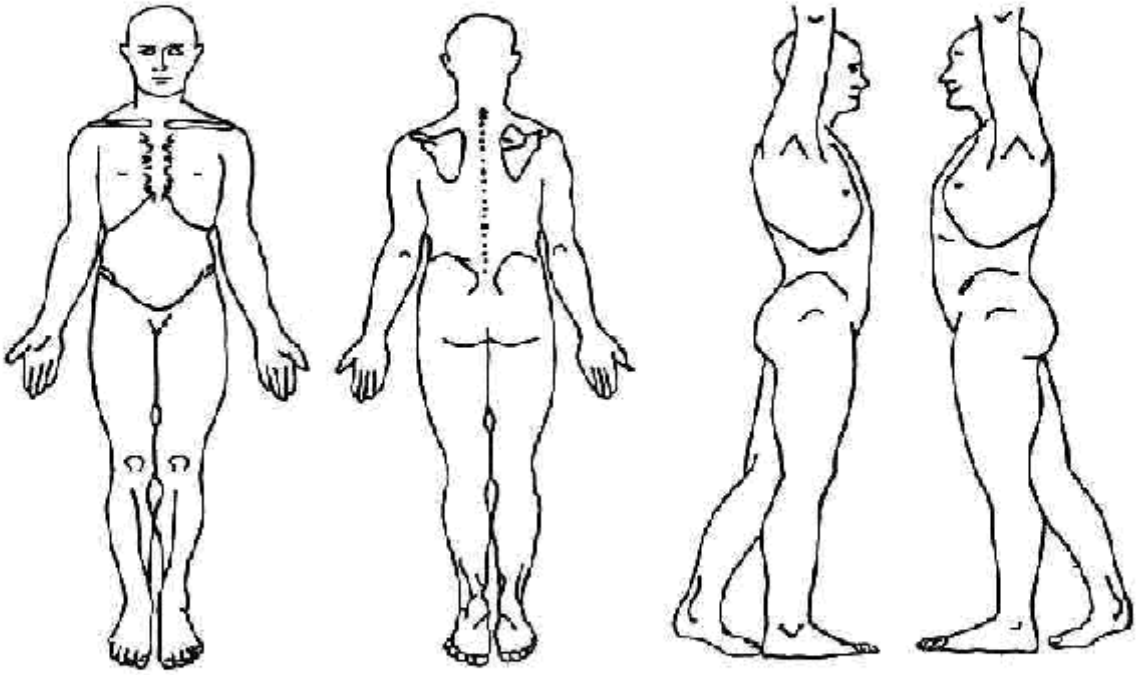
Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__| **Date:** __/__/____

Ctn EXAMINATION

Skin - location of lesions (body chart)
- type of lesions (patches, plaques, papules, nodules)
- signs of inflammation in lesions
- oedema of the hands and/or feet
- mark skin biopsy site, Date: __/__/____

Body Chart



	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions	None	Erythema	Erythema and raised	Ulceration	
A2	Number of raised and/or inflamed lesions	0	1-5	6-10	>10	
A3	Peripheral oedema due to reaction	None	Minimal	Visible, but not affecting function	Oedema affecting function	
A SCORE						

PRF completed by: _____ Date: _____ 16/111

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__| **Date:** __ / __ / ____

IF PATIENT HAS ENL–PHYSICIAN TO COMPLETE THE FOLLOWING ENL DATA COLLECTING FORM

Symptoms of ENL

How many days have you been feeling unwell for (this episode of ENL): ____ days

How unwell do you feel now (tick one face)?

Have you noticed….	NO	YES
Any new lumps on your skin?		
Any new sensory loss?		
Any new weakness in your muscles?		
Any new tingling?		
Any new pain in your joints?		
Any new pain in your bones?		
Any new pain in your testicles?		
Painful eyes?		
Any visual disturbance?		

Examination

Number of ENL lesions (circle): 0 1-5 6-20 >20

Inflammation in the ENL lesions (circle): None
Erythema and pain – function not affected
Erythema and pain – function affected
Erythema and pain – function affected plus ulceration

(If patient has previous records use comparison to previous VMT/ST testing):

VMT:	MRC=5	MRC=4	MRC=3	MRC<3
ST decreased in:	None	One nerve	Two nerve	≥ three nerves
Nerve tenderness: None	Tender on palpation		Withdraws	
Bone tenderness (shin):	None	Tender on palpation	Withdraws	
Oedema (ankle, face, hands):	None	Present	Gross	
Joint swelling:	None	Present	Affects function	
			Which: _____	
Lymph nodes:	Normal	Enlarged and tender		
Testicles:	Normal	Tender (? Size)		
Temperature:	≤37.5°C	>37.5°C	level: _____	
Proteinuria (by dipstick):	Negative	Positive	level: _____	
Red eyes:	Yes	No	Ophthalmology diagnosis:_____	

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__| **Date:** __/__/____

CONFIRM YOU HAVE SEEN AND ATTACHED VMT/ST FORM ☐

Describe any changes in VMT or ST compared to last assessment:

_____

_____

_____

Second Physician comment:

PATIENT HAS :

TYPE 1 REACTION ☐

ENL ☐

Specialist opinion on the severity of today's Reaction:

Severe ☐

Moderate ☐

Mild ☐

Comment and suggest normal therapy you would have prescribed:

.....

.....

.....

.....

NB: IF NERVE FUNCTION HAS WORSENED SINCE LAST REVIEW PLEASE LOOK AT PAGE 21 OF SOP FOR INDICATIONS FOR EXTRA PREDNISOLONE.

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__| **Date:** __/__/____

FORM: INVESTIGATIONS – physician to fill in

Laboratory tests **(record results if done)**

	Date taken dd/mm/yyyy	Result
FBC	--/--/----	Hb: |__|__|.|__| g/dl WCC: |__|__|__|__| Plt: |__|__|__|__| ESR |__|__|__|
Renal function	--/--/----	Creat: |__|__|.|__|__| mg/dl Urea |__|__|.|__| mg/dl K+: |__|__|.|__| meq/l Na: |__|__|.|__| meq/l Glucose |__|__|__| mg/dl
LFT	--/--/----	Alk phos |__|__|__| iu/l ASAT |__|__|__| iu/l ALAT |__|__|__| iu/l Bilirubin total |__|__|__| mg/dl
HIV Rapid test (via VCT)	--/--/----	1. Positive |__| 2. Negative |__|
Blood sugar (glucometer)	--/--/----	|__|__|
Stool for ova, cysts and parasites	--/--/----	1. Positive |__| 2. Negative |__|
Urinalysis (dipstick)	--/--/----	1. Positive |__| 2. Negative |__| Specify: _____
Pregnancy test (urine)	--/--/----	1. Positive |__| 2. Negative |__| Advise re contraception options

***EXTRA MEDICATION PRESCRIBED TODAY*:**

_____
_____
_____

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Week |__|__| **Date:** __/__/____

Record any adverse events here:

Type of adverse event	Date of onset	Date of resolution

Comments on management of adverse events:

_____
_____
_____
_____

Did the patient require hospital admission? 1.Yes ☐ 2. No ☐

If admitted was a SERIOUS ADVERSE EVENT FORM filled in?
1.Yes ☐ 2. No ☐

Was the DSMB notified 1.Yes ☐ 2. No ☐

What action was taken?

_____
_____
_____
_____

WHEN FINISHED:

COMPLETE PHARMACY CARD AND SEND PATIENT TO PHARMACY

Ciclosporin Studies (20.06.11) PRF completed by: _____ Date: _____ 20/111

Study: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

FORM 9: STUDY TERMINATION

Patient Hospital No: _____ Study number: _____

Termination date: ___/___/___

Form completed by:_____

This form must be completed for each patient upon leaving the study

1. Did the patient complete the full course of medication? ☐ No ☐ Yes

2. Did the patient receive additional Prednisolone? ☐ No ☐ Yes

If so, how many weeks (in total) did the patient receive Prednisolone? _____

3. Did the patient report for all examinations after treatment?

Week 24	☐ No	☐ Yes
Week 28	☐ No	☐ Yes
Week 32	☐ No	☐ Yes

4. If the patient did not complete the medication or the follow-up, select the reason:

- ☐ Subject did not return for clinic visit
- ☐ Protocol violation (specify) _____
- ☐ Subject refused study procedure(s): _____
- ☐ Voluntary withdrawal
- ☐ Illness (specify): _____
- ☐ Death: ___/___/___ (date)
- ☐ Other reason (specify): _____

Comments: _____
_____
_____

I have reviewed the contents of this case report form and found it to be complete and accurate.

Investigator's signature: _____ Date: _ _/_ _/_ _ _ _

APPENDIX 14: SERIOUS ADVERSE EVENT FORM

SERIOUS ADVERSE EVENT REPORT FORM
CICLOSPORIN STUDIES

PROTOCOL TITLE:	Protocol ID no:	Centre number:
	_____	___

Trial information

Randomisation number:	Investigation product:	Report type ☐ 1 = Initial 2 = Follow-up
____		

Adverse event information

1.Patient initials	2. Date of birth (dd/mm/yyyy)	3. Age (year)	4. Sex ☐ 1 = female 2 = male	5. Height (cm)	6.Weight (kg)	7.Event onset (dd/mm/yyyy)
	__/__/____			___	___._	__/__/____

8. Adverse event in MEDICAL TERMS:

Expedited report criteria (Tick all appropriate to event)

9.Patient died Date: (dd/mm/yyyy) / /	10. Life-threatening	11. Prolonged hospitalization	12. Significant disability	13. Congenital anomaly	14. Other SAE

15. Description:

.....
.....
.....
.....
.....
.....
.....

Suspected trial product information

16. Suspected product:	17. Daily dose at onset of event	18. Route of administration

19. Indication for use:

20.Therapy dates (dd/mm/yyyy) from: ____/____/_____ to: ____/____/_____

21. Did the event abate after stopping product? ☐ 1= No 2= Yes 3=NA

Concomitant drug(s)

22. Relevant concomitant drugs and dates of administration ☐ 1 = No 2 = Yes
If yes, then list the name(s) and details

Drug name	Dose / Route	Unit / Schedule	Date started (dd/mm/yyyy)	Continue 1 = No 2 = Yes	Date discontinued (dd/mm/yyyy)	Reason for use

Other relevant history, laboratory findings and action taken

23. Other relevant history:

.....

.....

.....

.....

.....

.....

.....

Relevant test/laboratory findings

Laboratory test	Unit	Date (dd/mm/yyyy)	Value	Comments on laboratory finding
		/ /		
		/ /		
		/ /		
		/ /		
		/ /		

25. Action taken by investigator:

0 = none
1 = Trial dosage change
3 = Trial drug discontinued
4 = Non-drug therapy
5 = Concomitant drug discontinued
6 = New drug therapy added
7 = Prolonged hospitalization

26. Outcome: ☐

1 = Completely recovered on (dd/mm/yyyy) ___/___/_____

2 = Recovered with sequel
3 = Condition improving
4 = Condition still unchanged
5 = Condition deteriorated
6 = Death, autopsy done (attach summary)
7 = Death, autopsy not done

27. Causality assessment by investigator (is there any relationship with test product?): ☐

0 = Not related
1 = Unlikely
2 = Possible
3 = Probable
4 = Most probable
5 = Insufficient data to assess

Has patient completed the study successfully? Yes ☐ No ☐

If no, what was the reason?

1. Withdrawal ☐
2. SAE ☐
3. Loss to follow up ☐
4. Other ☐ Specify:

_____

_____

_____

Last date patient was seen Date (dd/mm/yyyy): _____/_____/_____

Completion date Date (dd/mm/yyyy): _____/_____/_____

Information source	
28. Name, address, telephone and email address of the investigator Name: Profession (speciality) Address: Tel: _____Email: _____ Signature of investigator reporting event_____ Reporting date (dd/mm/yyyy) / /	
Sponsor information	
29. Name and address of Sponsor: Name: Address: _____ ____	
30. Date received by Sponsor (dd/mm/yyyy) Signature	32. Date of this report (dd/mm/yyyy) ____/____/_____

PI/Study Team Person Signature

.....

Date (dd/mm/yyyy): _____/_____/_____

APPENDIX 15: ETHICAL APPROVALS AND OTHER PERMITS

Ethical Approvals:

London School of Hygiene and Tropical Medicine x3

ALERT and AHRI Ethical Review Committee

National Ethics Review Committee

Drug Administration and Control Authority

Letters of collaboration LSHTM and ALERT

Clinical trials registration

Confirmation of clinical trial insurance

LONDON SCHOOL OF HYGIENE
& TROPICAL MEDICINE

ETHICS COMMITTEE

APPROVAL FORM
Application number: **5376**

Name of Principal Investigator	**Professor Diana Lockwood**
Department	**Infectious and Tropical Diseases**
Head of Department	**Professor Simon Croft**

Title: **Study 1: Ciclosporin in the management of Type 1 Reactions in Leprosy**

This application is approved by the Committee.

Chair of the Ethics Committee .....

Date .....

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form.

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

ETHICS COMMITTEE

APPROVAL FORM
Application number: **5377**

Name of Principal Investigator	**Professor Diana Lockwood**
Department	**Infectious and Tropical Diseases**
Head of Department	**Professor Simon Croft**

Title: **Study 2: Ciclosporin in the management of new Erythema Nodosum Leprosum**

This application is approved by the Committee.

Chair of the Ethics Committee .....[redacted].....

Date .....14 October 2008.....

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form.

LONDON SCHOOL OF HYGIENE
& TROPICAL MEDICINE

ETHICS COMMITTEE

APPROVAL FORM
Application number: **5378**

Name of Principal Investigator	**Professor Diana Lockwood**
Department	**Infectious and Tropical Diseases**
Head of Department	**Professor Simon Croft**

Title: **Study 3: Ciclosporin in the management of chronicor recurrent Erythema Nodosum Leprosum**

This application is approved by the Committee.

Chair of the Ethics Committee [redacted]

Date 9 October 2008

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form.

AHRI-ALERT ETHICAL REVIEW COMMITTEE APPROVAL SHEET

TITLE OF THE PROJECT

"A proposal for a group of liked research studies on the effectiveness of Cyclosporin in the treatment of leprosy reaction at ALERT Hospital, Addis Ababa."

PI: Saba Lambert

Project Reg. No. **P 005/08**

Recommendation of the AHRI-ALERT Ethics Review Committee

The above mentioned research project was duly considered by AHRI/ALERT Ethics Review Committee meeting on 17/06/08 and 13/01/09. The PI should submit progress report of the work every 6 months and the final report upon completion. The PI should also notify AAERC ahead any amendments or modifications in the protocol or premature suspension or termination of the study.

Signature: [redacted]

CHAIRPERSON

NAME: Dr Ruth Leekassa

Signature: [redacted]

SECRETARY

NAME: Ms Martha Zewdie

D/director of AHRI

Signature: [redacted]

Date: 26/5/09

Abraham Aseffa, MD, PhD
Deputy Director

Sponsored by the Governments of Ethiopia, Norway & Sweden
Armauer Hansen Research Institute

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የሳይንስና ቴክኖሎጂ ሚኒስቴር
The Federal Democratic Republic of Ethiopia
Ministry of Science and Technology

AHRI/ALERT
Addis Ababa

ቁጥር Ref. No: RDHE/34-90/2009
ቀን Date: 09 DEC 2009

Re: A proposal for a group of liked research studies on the effectiveness of cyclosporine in the treatment of Leprosy reaction at ALERT Hospital, Addis Ababa, and Ethiopia

Dear Sir/Mr./s/Dr.

The National Health Research Ethics Review Committee (NERC) has reviewed the aforementioned project proposal with special emphasis on the following points

1. Are all ethical principles considered?
   - 1.1 Respect for persons — Yes ☑ No ☐
   - 1.2 Beneficence — Yes ☑ No ☐
   - 1.3 Justice — Yes ☑ No ☐

2. Are the objectives of the study ethically achievable? Yes ☑ No ☐

   Are/Is methods ethically sound? Yes ☑ No ☐

Based on the above mentioned ethical assessment NERC has

a) **Approved** the proposal for implementation ☑
   Expiry date of the review

09	December	2010
Date	Month	Year

b) Conditionally approved ☐
c) Not approved ☐

Finally we would like to take this opportunity to request your good office to monitor the ethical implementation of the project as stipulated in the original project document defined as VERSION 20/05/09 Information Sheet Cyclosporine/Type 1-Reaction. It is also explicitly advice you to submit a periodical progressive report to the NERC Secretariat Office.

With regards,

[redacted]

Feleke Kibret
Secretary of NERC

The Federal Democratic Republic of Ethiopia Ministry of Science and Technology

CC. Dr. Saba Maria Lambert
AHRI/ALERT
Addis Ababa

ማነጋገር ቢያስፈልግዎ
You may Contact

ፖ.ሳ.ቁ P.O.Box 2490
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e-mail most@ethionet.et
ስልክ Tel. 251-011-156 21 55
web site:-http// www.most.gov.et
ፋክስ Fax 251-011-1-56 27 49

በኢትዮጵያ ፌዴራላዊ ዴሞክራሲያዊ ሪፐብሊክ
THE FEDERAL DEMOCRATIC REPUBLIC OF ETHIOPIA
የኢትዮጵያ የመድኃኒት አስተዳደርና ቁጥጥር ባለሥልጣን
DRUG ADMINISTRATION AND CONTROL AUTHORITY OF ETHIOPIA

ቁጥር 02/12/701/926
Ref. No.

ቀን 12 MAY 2010
Date:

AHRI/ALERT

Addis Ababa

Subject: Clinical Trial Authorization

Your application to conduct clinical trial entitled "***Effectiveness of Ciclosporin in the Treatment of Leprosy Reactions***" was evaluated and authorized.

The clinical trial authorization is subjected to the following conditions:

1. The clinical trial shall be conducted in accordance with the protocol submitted to the Authority. Any amendments to the protocol shall first be submitted to the Authority for approval.
2. The Authority shall be informed immediately of any severe adverse effects or death, which may occur during the clinical trial and any data, received which might cause doubt on the validity of the continuation of the study.
3. The Authority shall be informed of any decision to discontinue the clinical trial. The reason for such discontinuation must be stated.
4. The Authority shall be informed an interim report(at least twice in a year)
5. The Authority shall inspect the clinical trial site at any time for compliance to the Good Clinical Trial Practice.

Best Regards

[redacted]

ESTIFANIT MENGISTU
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ዳይሬክቶሬት ዳይሬክተር
Director, Product Registration & Licensing Directorate

CC

- Product Registration And Licensing Directorate

DACA

ፋክስ/Fax: 251-1-52 13 92 P.O.Box: 5681 Tel: 251-1-52 41 22/52 41 23 E-mail: daca@telecom.net.et
መልስ በሚሰጡበት ጊዜ የእኛን ደብዳቤ ቁጥር ይጥቀሱ
IN REPLY REFER TO OUR Ref. No.

London School of Hygiene & Tropical Medicine
(University of London)

Keppel Street, London WC1E 7HT
Tel: +44 (0) 7927-2304 direct line
Fax +44 (0)20 7637 4314
E-mail: alison.grant@lshtm.ac.uk
Department of Infectious and Tropical Diseases
Clinical Research Unit

1899 1999
contributing to health worldwide

4th March 2009

ALERT/AHRI Ethical Review Committee
ALERT

Dear Sir/Madam,

Study: **Effectiveness of ciclosporin in the treatment of leprosy reactions at ALERT Hospital, Addis Ababa, Ethiopia**

This is a letter of support confirming the London School of Hygiene & Tropical Medicine is willing to co-operate in issues concerning the above study which is being led by Dr Saba Maria Lambert, under the supervision of Professor Diana Lockwood in local collaboration with ALERT Hospital and AHRI.

Yours faithfully,

[redacted]

Alison Grant
Head, Clinical Research Unit

cc Dr Saba M. Lambert

ALERT

L AFRICA LEPROSY, TUBERCULOSIS AND REHABILITATION TRAINING CENTRE

Ref. No. ኧኮ2923/ሐጥ-0090/2009
ETC
Date 20-03-2009
ዓ.ም

To: ALERT/AHRI ETHICAL REVIEW COMMITTEE

ALERT

ISSUE: SUPPORT LETTER

This letter acts as a support letter confirming that our hospital is willing to co-operate in all possible issues concerning the study led by Dr Saba Maria Lambert, under the supervision of Professor Diana Lockwood of the London School of Hygiene and Tropical Medicine, and with local collaboration with ALERT Hospital and AHRI.

The study is titled: Effectiveness of Ciclosporin in the treatment of Leprosy Reactions at ALERT Hospital, Addis Ababa, Ethiopia

With regards,

[redacted]

Dr. Yirgalem Abebe

ALERT Hospital Service
Acting Medical Director

Cc Dr Saba M. Lambert

ERT
).Box 165
DIS ABABA
HIOPIA

Executive Director (+251-1) 21 13 37
Training Division 21 13 41
Medical Department 21 13 38
Administration 21 13 36
AHRI 21 13 32
Switch Board 21 13 35

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E-mail: leprosytb@telecom.net.et
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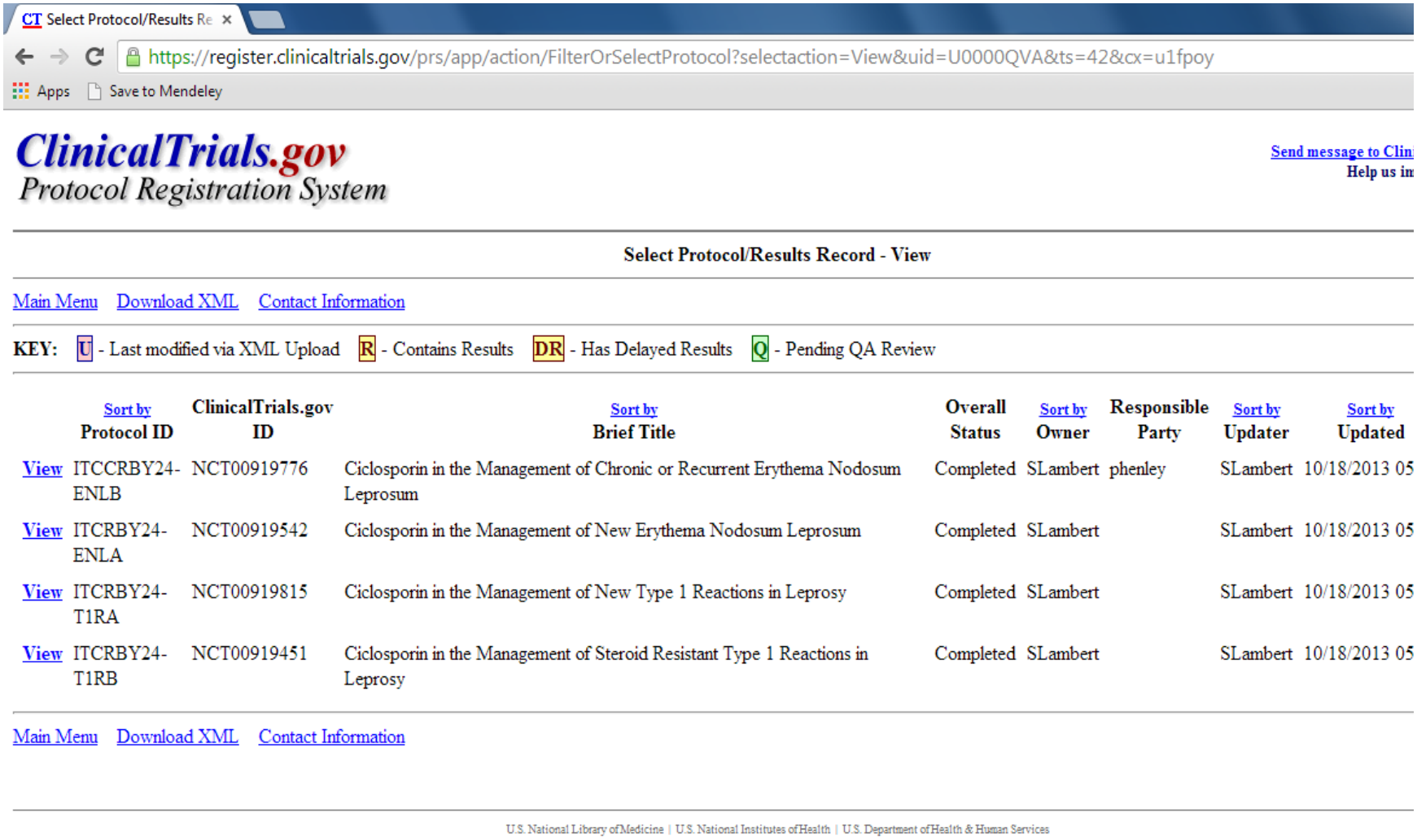

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https://register.clinicaltrials.gov/prs/app/action/FilterOrSelectProtocol?selectaction=View&uid=U0000QVA&ts=42&cx=u1fpoy

Apps Save to Mendeley

ClinicalTrials.gov
Protocol Registration System

Send message to Clin
Help us im

Select Protocol/Results Record - View

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KEY: U - Last modified via XML Upload R - Contains Results DR - Has Delayed Results Q - Pending QA Review

	Sort by Protocol ID	ClinicalTrials.gov ID	Sort by Brief Title	Overall Status	Sort by Owner	Responsible Party	Sort by Updater	Sort by Updated
View	ITCCRBY24-ENLB	NCT00919776	Ciclosporin in the Management of Chronic or Recurrent Erythema Nodosum Leprosum	Completed	SLambert	phenley	SLambert	10/18/2013 05
View	ITCRBY24-ENLA	NCT00919542	Ciclosporin in the Management of New Erythema Nodosum Leprosum	Completed	SLambert		SLambert	10/18/2013 05
View	ITCRBY24-T1RA	NCT00919815	Ciclosporin in the Management of New Type 1 Reactions in Leprosy	Completed	SLambert		SLambert	10/18/2013 05
View	ITCRBY24-T1RB	NCT00919451	Ciclosporin in the Management of Steroid Resistant Type 1 Reactions in Leprosy	Completed	SLambert		SLambert	10/18/2013 05

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London School of Hygiene & Tropical Medicine
Research Grants & Contracts Office
Keppel Street, London WC1E 7HT

Tel +44 (0) 20 7927 2525 (direct) Fax +44 (0) 20 7580 5636
e-mail: patricia.henley@lshtm.ac.uk
www.intra.lshtm.ac.uk/trials

Our ref: QA176

15 June 2005

Professor Diana Lockwood
CRU, ITD
LSHTM

Dear Professor Lockwood,

Re: Study 1a: Ciclosporin in the management of new Type 1 Reactions in Leprosy
Study 1b: Ciclosporin in the management of steroid resistant Type 1 Reactions in Leprosy

As the authorised representative for the London School of Hygiene & Tropical Medicine (LSHTM), I can confirm that LSHTM will act as the identified Research Sponsor the organisation which takes responsibility for the initiation management, and/or financing of a clinical trial, for the above titled project. I can confirm that the research proposal has been reviewed, assessed and registered by the Clinical Trials Sub-Committee

It is the Chief Investigator's responsibility to ensure that members of the research team comply with all local regulations applicable to the performance of the project including, but not limited to, the Declaration of Helsinki (2008), ICH Good Clinical Practice Guidelines (1996), and for projects conducted in the UK the Medicines for Human Use (Clinical Trials) Regulations (2004), the Research Governance Framework for Health and Social Care (2005), the Data Protection Act (1998) and the Human Tissue Act (2004).

LSHTM carries Non Negligent Harm Insurance and Professional Negligence Insurance applicable to this study:

	Non Negligent Compensation	Medical Malpractice
Insurer	Lloyds (Marked cm')	Lloyds (MarketForm)
Certification No.	05/3047302	05/0004/305
Finance Cover	£3 million pounds sterling(excluding HIV)	£7.5 million pounds sterling

The Non-Negligent Harm policy is worldwide with the exception of the United States and Canada. This policy is subject to terms, conditions and exceptions.

LSHTM Sponsorship is conditional on the project receiving applicable ethical and regulatory approval as well as successful contract and agreement negotiations from the Research Grants and Contracts Office where relevant, before the study commences.

A copy of the ethics and regulatory approval letters must be sent to the Clinical Trials QA Manager prior to the study commencing. Sponsorship is dependent on obtaining local approval for all sites where the research is being conducted. It is recommended that all members of the study team attend Good Clinical Practice (GCP) training every two years.

Yours sincerely,

[redacted]

Patricia Henley
Clinical Trials QA Manager
on behalf of the Clinical Trials Sub-Committee

London School of Hygiene & Tropical Medicine
Research Grants & Contracts Office
Keppel Street, London WC1E 7HT

Tel +44 (0) 20 7927 2625 (direct) Fax +44 (0) 20 7580 5636
e-mail: patricia.henley@lshtm.ac.uk
www.intra.lshtm.ac.uk/trials

Our ref: QA176 and QA177

15 June 2009

Professor Diana Lockwood
CRU, ITD
LSHTM

Dear Professor Lockwood,

Re: **Study 2a: Ciclosporin in the management of new Erythema Nodosum Leprosum**
Study 2b: Ciclosporin in the management of chronic or recurrent Erythema Nodosum Leprosum

As the authorised representative for the London School of Hygiene & Tropical Medicine (LSHTM), I can confirm that LSHTM will act as the identified Research Sponsor, the organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial for the above titled project. I can confirm that the research proposal has been reviewed, assessed and registered by the Clinical Trials Sub-Committee.

It is the Chief Investigator's responsibility to ensure that members of the research team comply with all local regulations applicable to the performance of the project, including, but not limited to: the Declaration of Helsinki (2008), ICH Good Clinical Practice Guidelines (1996) and for projects conducted in the UK: the Medicines for Human Use (Clinical Trials) Regulations (2004), the Research Governance Framework for Health and Social Care (2005), the Data Protection Act (1998) and the Human Tissue Act (2004).

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	Non Negligent Compensation	Medical Malpractice
Insurer	Lloyds (MarketForm)	Lloyds (MarketForm)
Certification No.	05/0047302	05/0047305
Finance Cover	£3 million pounds sterling(excluding HIV)	£7.5 million pounds sterling

The Non-Negligent harm policy is worldwide, with the exception of the United States and Canada. The policy is subject to terms, conditions and exceptions

LSHTM Sponsorship is conditional on the project receiving applicable ethical and regulatory approval as well as successful contract and agreement negotiations from the Research Grants and Contracts Office, where relevant, before the study commences

A copy of the ethics and regulatory approval letters must be sent to the Clinical Trials QA Manager prior to the study commencing. Sponsorship is dependent on obtaining local approval for all sites where the research is being conducted. It is recommended that all members of the study team attend Good Clinical Practice (GCP) training every two years.

Yours sincerely,

[redacted]

Patricia Henley
Clinical Trials QA Manager
on behalf of the Clinical Trials Sub Committee

APPENDIX 16: GOOD CLINICAL PRACTICE COURSE TIMETABLE

Good Clinical Practice Training
Clinical Trial: Ciclosporin in Leprosy Reaction
LSHTM/ ALERT/AHRI
Addis Ababa, Wednesday August 4th and Thursday August 5th, 2010
1-4:35pm at ALERT Training Centre

Day 1: General GCP day

1:00pm - 1:10pm	Registration, Welcome and Introduction	Dr Saba Lambert
1:10pm - 1: 20pm	Opening address	Dr Andargachew
1:20pm - 1:50pm	Principles of GCP: subject right, safety and well-being	Dr Ahmed Bedru
1:50pm – 2:20pm	Role and responsibilities of Investigator , sponsor and DSMB	Dr Jemal Hussein
2:20pm – 2:50pm	Safety reporting mechanism	Dr Saba Lambert
2:50pm – 3:05pm	**Coffee Break**	
3:05pm – 3:35pm	Data Management and CRF (Monitoring, Audit and Inspection in brief)	Dr Lawrence Yamuah
3:35pm – 4:05pm	Informed consent process	Dr Shimeless
4:05pm – 4:35pm	Discussion	

Day 2: Ciclosporin Study Specific day

1:00pm – 2:00pm	Ciclosporin Study Protocol Background information, Trial Objectives and Trial design, Selection criteria and Treatment of subjects Side Effects and Adverse events	Dr Saba Lambert
2:00pm – 2:30pm	Investigational product management procedure Randomization procedure Treatment distribution	Asegid Alem Tura
2:30pm – 2:50pm	Laboratory specimen procedure and Pathology	Dr Jemal Hussein
2:50pm – 3:10 pm	**Coffee Break**	
3:10pm – 3:30 pm	Clinical Record Form with physio demonstration	Dr Digafe
3:30pm – 4:00pm	Other – QOL questionnaire, Severity Scale T1R, ENL scoring, Feed-back on Informed consent forms	Dr Saba Lambert
4:00pm -4:30pm	**Discussion**	

Day 3: Afternoon visit to St Peter's Hospital (date to be specified)

Participants:

Name	**Role**	**Tel**	**Email**
Dr Elsa Bizuneh	Dermatologist	0911 401545	elizabeth_kassa@yahoo.com
Dr Shimeless	Dermatologist	0911 642060	shim_8000@yahoo.com
Dr Digafe	Dermatologist	0911 407695	digafe2003@yahoo.com
Dr Saba Lambert	Clinical Researcher	0911 82 4438	sabalambert@hotmail.com
Dr Ahmed Bedru	AHRI Trial co-ordinator	0911 405405	ahmedsebah2002@yahoo.com
Dr Jemal Hussein	AHRI Pathologist	0911 248265	jemaldr@gmail.com
Dr Lawrence Yamuah	AHRI Data Management	0911 608706	yamuahlk@yahoo.co.uk
Nurse Captain	RMC nurse	0912 183688	
Nurse Abebe	RMC nurse	0912097678	
Nurse Solomon	RMC nurse		
Hanna	RMC runner		
	RMC runner		
Nurse Getachew	Social worker/counsellor		
Demisew Yiheyis	Physio	0913 181736	
Temeru Wakshum	Physio	0911 934689	
Asegid Alem Tura	Pharmacy	0913 383235	asegidalemutura@yahoo.com
Andargachew Gashu	Laboratory	0911 192751	
Sr Guenet	AHRI-Biopsy nurse	0911 214208	
Jemal Ahmed	AHRI- Biopsy nurse		
Kiros Ayenew	Pathology technician		
W/o Banchayehu Gualu	Pathology technician		

Dr Fuad Temam	Dermatologist -**DSMB committee**	0911 234937	fuadtemam@yahoo.com
Ato Sileshi Fanta	Statistician – **DSMB committee**	0911 483921	sileshifanta@yahoo.com
Dr Getenet Yimer	**DSMB committee**	0911 405387	getnetyimer@yahoo.com
Martha	Trial Monitor		

Email list:

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APPENDIX 17: PHARMACY- MEDICATION DISPENSING CARDS

CnT1RA **CICLOSPORIN ARM** **Weight range: 30-39kg**

Participant Study number	
Participant name	
Alert Clinic Card number	

Enrolment date:	
Patient weight:	

					CICLOSPORIN			PRED + PLACEBO			Daily regimen						Extra Prednisolone	
	Date of Tx issue	Next review date	Supply of Tx	Patient weight in kg	Ciclosporin /kg	Cn daily dosage dosage	Cn caps 50mg daily	Predn	5mg Predn tab	Placebo Pn tab-am dose	Tablets am			tabs pm	Tot n tab/day		Date	Dose
											Pn	PnPl	Cn	Cn				
Week 0			14 days		7.5mg/kg	250mg	5	40mg	8	0	8	0	3	2	13			
					7.5mg/kg	250mg	5	40mg	8	0	8	0	3	2	13			
Week 2			14 days		7.5mg/kg	250mg	5	20mg	4	3	4	3	3	2	12			
					7.5mg/kg	250mg	5	10mg	2	5	2	5	3	2	12			
Week 4			14 days		7.5mg/kg	250mg	5		0	6	0	6	3	2	11			
					7.5mg/kg	250mg	5		0	6	0	6	3	2	11			
Week 6			14 days		7.5mg/kg	250mg	5		0	5	0	5	3	2	10			
					7.5mg/kg	250mg	5		0	5	0	5	3	2	10			
Week 8			28 days		7.5mg/kg	250mg	5		0	4	0	4	3	2	9			
					7.5mg/kg	250mg	5		0	4	0	4	3	2	9			
					7.5mg/kg	250mg	5		0	4	0	4	3	2	9			
					7.5mg/kg	250mg	5		0	4	0	4	3	2	9			
Week 12			28 days		6mg/kg	200mg	4		0	3	0	3	2	2	7			
					6mg/kg	200mg	4		0	3	0	3	2	2	7			
					6mg/kg	200mg	4		0	3	0	3	2	2	7			
					6mg/kg	200mg	4		0	3	0	3	2	2	7			
Week 16			28 days		4mg/kg	150mg	3		0	2	0	2	2	1	5			
					4mg/kg	150mg	3		0	2	0	2	2	1	5			
					2mg/kg	100mg	2		0	1	0	1	1	1	3			
					2mg/kg	100mg	2		0	1	0	1	1	1	3			
Week 20			X	Remarks:														
Week 24			X															
Week 28			X															
Week 32			X															

CnT1RA **PREDNISOLONE ARM** **Weight range: 30-39kg**

Participant Study number	
Participant name	
Alert Clinic Card number	

Enrolment date:	
Patient weight (kg):	

	Date of Tx issue	Next review date	Supply of Tx	Patient weight in kg	Prednisolone	# of Pred 5mg tab /day *	Plac Cn 50mg tab /day *	Daily Regimen				Extra Predn
								Tablets am		tablets pm	Tot n tab /day	Date
								Pn	Cn plac	Cn plac		
Week 0			14 days		40mg	8	5	8	3	2	13	
					40mg	8	5	8	3	2	13	
Week 2			14 days		35mg	7	5	7	3	2	12	
					35mg	7	5	7	3	2	12	
Week 4			14 days		30mg	6	5	6	3	2	11	
					30mg	6	5	6	3	2	11	
Week 6			14 days		25mg	5	5	5	3	2	10	
					25mg	5	5	5	3	2	10	
Week 8			28 days		20mg	4	5	4	3	2	9	
					20mg	4	5	4	3	2	9	
					20mg	4	5	4	3	2	9	
					20mg	4	5	4	3	2	9	
Week 12			28 days		15mg	3	4	3	2	2	7	
					15mg	3	4	3	2	2	7	
					15mg	3	4	3	2	2	7	
					15mg	3	4	3	2	2	7	
Week 16			28 days		10mg	2	3	2	2	1	5	
					10mg	2	3	2	2	1	5	
					5mg	1	1	1	1	1	3	
					5mg	1	1	1	1	1	3	
Week 20			X	Remarks:								
Week 24			X									
Week 28			X									
Week 32			X									

CnT1RA **CICLOSPORIN ARM** **Weight range: 50-59kg**

Participant Study number	
Participant name	
Alert Clinic Card number	

Enrolment date:	
Patient weight:	

					CICLOSPORIN			PRED + PLACEBO			Daily regimen						Extra Prednisolone	
	Date of Tx issue	Next review date	Supply of Tx	Patient weight in kg	Ciclosporin /kg	Cn daily dosage dosage	Cn caps 50mg daily	Predn	5mg Predn tab	Placebo Pn tab-am dose	Tablets am			tabs pm	Tot n tab/day		Date	Dose
											Pn	PnPl	Cn	Cn				
Week 0			14 days		7.5mg/kg	400mg	8	40mg	8	0	8	0	4	4	16			
					7.5mg/kg	400mg	8	40mg	8	0	8	0	4	4	16			
Week 2			14 days		7.5mg/kg	400mg	8	20mg	4	3	4	3	4	4	15			
					7.5mg/kg	400mg	8	10mg	2	5	2	5	4	4	15			
Week 4			14 days		7.5mg/kg	400mg	8		0	6	0	6	4	4	14			
					7.5mg/kg	400mg	8		0	6	0	6	4	4	14			
Week 6			14 days		7.5mg/kg	400mg	8		0	5	0	5	4	4	13			
					7.5mg/kg	400mg	8		0	5	0	5	4	4	13			
Week 8			28 days		7.5mg/kg	400mg	8		0	4	0	4	4	4	12			
					7.5mg/kg	400mg	8		0	4	0	4	4	4	12			
					7.5mg/kg	400mg	8		0	4	0	4	4	4	12			
					7.5mg/kg	400mg	8		0	4	0	4	4	4	12			
Week 12			28 days		6mg/kg	300mg	6		0	3	0	3	3	3	9			
					6mg/kg	300mg	6		0	3	0	3	3	3	9			
					6mg/kg	300mg	6		0	3	0	3	3	3	9			
					6mg/kg	300mg	6		0	3	0	3	3	3	9			
Week 16			28 days		4mg/kg	200mg	4		0	2	0	2	2	2	6			
					4mg/kg	200mg	4		0	2	0	2	2	2	6			
					2mg/kg	100mg	2		0	1	0	1	1	1	3			
					2mg/kg	100mg	2		0	1	0	1	1	1	3			
Week 20			X	Remarks:														
Week 24			X															
Week 28			X															
Week 32			X															

CnT1RA **PREDNISOLONE ARM** **Weight range: 50-59kg**

Participant Study number	
Participant name	
Alert Clinic Card number	

Enrolment date:	
Patient weight (kg):	

	Date of Tx issue	Next review date	Supply of Tx	Patient weight in kg	Prednisolone	# of Pred 5mg tab /day *	Plac Cn 50mg tab /day *	Daily Regimen				Extra Predn
								Tablets am		tablets pm	Tot n tab /day	Date
								Pn	Cn plac	Cn plac		
Week 0			14 days		40mg	8	8	8	4	4	16	
					40mg	8	8	8	4	4	16	
Week 2			14 days		35mg	7	8	7	4	4	15	
					35mg	7	8	7	4	4	15	
Week 4			14 days		30mg	6	8	6	4	4	14	
					30mg	6	8	6	4	4	14	
Week 6			14 days		25mg	5	8	5	4	4	13	
					25mg	5	8	5	4	4	13	
Week 8			28 days		20mg	4	8	4	4	4	12	
					20mg	4	8	4	4	4	12	
					20mg	4	8	4	4	4	12	
					20mg	4	8	4	4	4	12	
Week 12			28 days		15mg	3	6	3	3	3	9	
					15mg	3	6	3	3	3	9	
					15mg	3	6	3	3	3	9	
					15mg	3	6	3	3	3	9	
Week 16			28 days		10mg	2	4	2	2	2	6	
					10mg	2	4	2	2	2	6	
					5mg	1	2	1	1	1	3	
					5mg	1	2	1	1	1	3	
Week 20			X	Remarks:								
Week 24			X									
Week 28			X									
Week 32			X									

CnENL **CICLOSPORIN ARM (Study A and B)** **Weight range: 60-69kg**

Participant Study number	
Participant name	
Alert Clinic Card number	

Enrolment date:	
Patient weight:	

					CICLOSPORIN			PRED + PLACEBO			Daily regimen					Extra Predn
	Date of Tx issue	Next Review Date	Supply of tx - days	Patient weight in kg	Ciclosporin /kg	Cn daily dose (mg)	Cn caps 50mg daily	Predn	5mg Predn tab	Placebo Pn tab- am dose	Tablets am			Tablets pm	Tot n tab/ day	Date
											Pn	PnPl	Cn	Cn		
Week 0			14 days		7.5mg/kg	500	10	40mg	8	4	8	4	5	5	22	
					7.5mg/kg	500	10	40mg	8	3	8	3	5	5	21	
Week 2			14 days		7.5mg/kg	500	10	20mg	4	6	4	6	5	5	20	
					7.5mg/kg	500	10	10mg	2	7	2	7	5	5	19	
Week 4			14 days		7.5mg/kg	500	10		0	8	0	8	5	5	18	
					7.5mg/kg	500	10		0	7	0	7	5	5	17	
Week 6			14 days		7.5mg/kg	500	10		0	6	0	6	5	5	16	
					7.5mg/kg	500	10		0	5	0	5	5	5	15	
Week 8			28 days		7.5mg/kg	500	10		0	4	0	4	5	5	14	
					7.5mg/kg	500	10		0	4	0	4	5	5	14	
					7.5mg/kg	500	10		0	3	0	3	5	5	13	
					7.5mg/kg	500	10		0	3	0	3	5	5	13	
Week 12			28 days		6mg/kg	400	8		0	2	0	2	4	4	10	
					6mg/kg	400	8		0	2	0	2	4	4	10	
					4mg/kg	250	5		0	1	0	1	3	2	6	
					2mg/kg	150	3		0	1	0	1	2	1	4	
Week 16			X	Remarks:												
Week 20			X													
Week 24			X													
Week 28			X													
Week 32			X													

CnENL **PREDNISOLONE ARM (Study A & B)** **Weight range: 60-69kg**

Participant Study number		
Participant name		
Alert Clinic Card number		

Enrolment date	
Patient weight (kg)	

	Date of Tx issue	Next Review Date	Supply of tx -days	Patient weight in kg	Prednisolone	# of Pred 5mg tab /day *	Plac Cn 50mg tab /day *
Week 0			14 days		60mg	12	10
					55mg	11	10
Week 2			14 days		50mg	10	10
					45mg	9	10
Week 4			14 days		40mg	8	10
					35mg	7	10
Week 6			14 days		30mg	6	10
					25mg	5	10
Week 8			28 days		20mg	4	10
					20mg	4	10
					15mg	3	10
					15mg	3	10
Week 12			28 days		10mg	2	8
					10mg	2	8
					5mg	1	5
					5mg	1	3
Week 16			X	Remarks:			
Week 20			X				
Week 24			X				
Week 28			X				
Week 32			X				

Daily Regimen			
Tablets am		Tablets pm	Tot n tab /day
Pn	Cn placebo	Cn placebo	
12	5	5	22
11	5	5	21
10	5	5	20
9	5	5	19
8	5	5	18
7	5	5	17
6	5	5	16
5	5	5	15
4	5	5	14
4	5	5	14
3	5	5	13
3	5	5	13
2	4	4	10
2	4	4	10
1	3	2	6
1	2	1	4

Extra Prednisolone	
Date	Dose

APPENDIX 18: CICLOSPORIN GMP CERTIFICATE AND IMPORT PERMIT

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Jai Shankar
Regulatory Concepts Pty Ltd
Unit 9/ 7 Anella Avenue
CASTLE HILL NSW 2154

Sponsor Client ID: 23985

Application on behalf of: Helex-A Pty Ltd
Unit 9 / 7 Anella Avenue
CASTLE HILL NSW 2154

GMP Clearance Application MI-2009-CL-04564-3 Notification.

Please be advised that GMP Clearance is approved for the following manufacturer:

Panacea Biotec Ltd
Malpur Baddi
Tehsil Nalagarh Solan Dist Himachal Pradesh 173205
India

Manufacturer Client ID: 53449

Manufacturing Type	Sterility	Dosage Form	Product Category	Manufacturing Step
Medicine manufacture	Non Sterile	Solid Unit Dosage Forms - Hard Capsules	Registered Therapeutic Good	Finished Product Manufacture
Medicine manufacture	Non Sterile	Capsules, soft	Registered Therapeutic Good	Finished Product Manufacture
Medicine manufacture	Non Sterile	Solid Unit Dosage Forms - Tablets	Registered Therapeutic Good	Finished Product Manufacture

This Clearance remains current until 30/01/2012 unless otherwise revoked.

You are advised to submit a new electronic GMP Clearance application with updated GMP evidence prior to the expiry date to avoid delays in the registration/listing of new products and maintain products on the Australian Register of Therapeutic Goods (ARTG). Expired GMP Clearance could result in affected product(s) being removed from the ARTG.

THIS CLEARANCE LETTER IS ISSUED BY TGA FOR FUTURE LISTING/REGISTRATION OF THE PRODUCT TYPES SPECIFIED ABOVE.

For further information please refer to the Therapeutic Goods Administration website: http://www.tga.gov.au, alternatively you may contact the undersigned.

Yours sincerely
[redacted]
Evgeny Clifford
GMP Clearance Unit
Office of Manufacturing Quality
Therapeutic Goods Administration
23/11/2009

Address: PO Box 100 Woden ACT 2606 Website: www.tga.gov.au
Telephone: Main Data Point (02 6232 8163), Callers Outside (06 6232 8078), Query Regarding (02 6272 8812)

DRUG CONTROLLING CUM DRUG LICENSING AUTHORITY, HEALTH AND FAMILY WELFARE DEPARTMENT, SDA COMPLEX, KASUMPATI, SHIMLA – 171 009 (H.P.)

CERTIFICATE OF A PHARMACEUTICAL PRODUCT[1]

(This Certificate conforms to the format recommended by the World Health Organisation)

No. of Certificate : MB/05/203/WHO/GMP/36
Exporting (Certifying) Country : INDIA
Importing (requesting) Country : ALL COUNTRIES

1. Name and dosage form of Product:

Generic Name : **Cyclosporine Capsules USP 25 mg**

Brand Name : Panimun Bioral 25 mg

Dosage Form : **Capsules (soft gelatin)**

1.1 Active ingredient(s)[2] and amount(s) per unit dose[3]:
(Including Excipients as declared by the firm)[4]

Composition: Each soft gelatin capsule contains:

	Quantity/ Unit
Cyclosporine USP	25 mg
Colour: Ferric Oxide (Red)	

Excipients:
Propylene Glycol USP+IH
Polyoxyl 40 Hydrogenated Castor Oil USNF+IH
Propylene Glycol Monolaurate USNF+IH
Gelatin USNF+IH
Gelatin (Low Molecular Weight) IH
Maltitol Solution USNF IH
Glycerin USP+IH
Purified Water USP+IH
Ferric Oxide (Red) USNF IH
Soybean Oil USP+IH
Opaspade WB (White) IH

1.2. Is this product licensed to be placed on the market for the use in the exporting country?[5] ✓**Yes**/No.
(Key in as appropriate)
(If Yes, continue with the section 2A and omit section 2B
If 'No', omit section 2A & continue with section 2B)[6]

1.3. Is this product actually on the market in the exporting country?
✓**Yes**/No (Key in as appropriate)

[4] Ingredients for which, specifications other than IP are mentioned are either meant for export or are not official in IP. For Indian market, ingredients official in IP shall be used whereas for export market BP/USP/USNF/IH excipients shall be used.

2 A 1 No. of Product licence[7] & date of issue:
Mfg. Lic. No. **MB/05/203**. Date of permission to manufacture the product: **20.06.2006**

የኢትዮጵያ የምግብ፣ የመድኃኒትና የጤና ክብካቤ
አስተዳደርና ቁጥጥር ባለሥልጣን
FOOD, MEDICINE AND HEALTH CARE
ADMINISTRATION AND CONTROL AUTHORITY OF
ETHIOPIA

ቁጥር
Ref. No. 02/16/09/118

ቀን
Date: 21/04/2011

To AHRI/ALERT

Addis Ababa

Subject: Drug import permit

With reference to the issued clinical trial authorization letter reference number 02/12/70/926, dated April 5th, 2011 study title "**effectiveness of ciclosporin in the treatment of leprosy reactions**" you have requested amendment of import permit of drugs from previously 25 mg to 50 mg because of the pill burden for patients to take ciclosporin 25 mg capsule that is used to conduct the study. Hence, you are authorized to import the drug used in the study **ciclosporin 50 mg** in a quantity of 15,000 pack of 6 capsules and 12,000 packs of **placebo capsules** from **Panacea-Biotec, India**.

We inform all the concerned parties in the custom clearance of the drug import permit and ask for their cooperation.

Best regards,

[redacted]

Director, Product Registration &
Licensing Directorate

ቁጥር/Fax: 251-1-52 13 92 P.O.Box: 5681 Tel: 251-1-52 41 22/52 41 23 E-mail: dacs@telecom.net.et
መልስ በሚሰጠበት ጊዜ የእኛን ደብዳቤ ቁጥር ይጥቀሱ
IN REPLY REFER TO OUR Ref. No.

APPENDIX 19: PREDNISOLONE AND PLACEBO TEST RESULTS

April 2010

Determine the quality of prednisolone and placebo control tablets submitted for analysis by Dr S Lambert following their dissolution profile.

Background:

Prednisolone (5 mgs) and placebo tablets were analysed by following the method specified in the USP 24 for the dissolution profile of the drug; pages 1539-1540. The method uses the dissolution apparatus followed by high performance liquid chromatography analysis (HPLC).

Procedure:

Tablets (n=4 of each placebo and authentic active principal ingredient) were placed in the containers and 900 ml of degassed water added to each. Aliquots were collected for analyses on HPLC at 10 min intervals for an hour. The steps then followed to authenticate and measure the detected peak were to compare with the commercial standard:

1. The elution time of the peak at 2.5 min, figure 1.
2. The absorbance spectra with a maxima at 245.5 nm, figure 2.
3. The amount of active ingredient was determined from the calibration curve, figure 3.

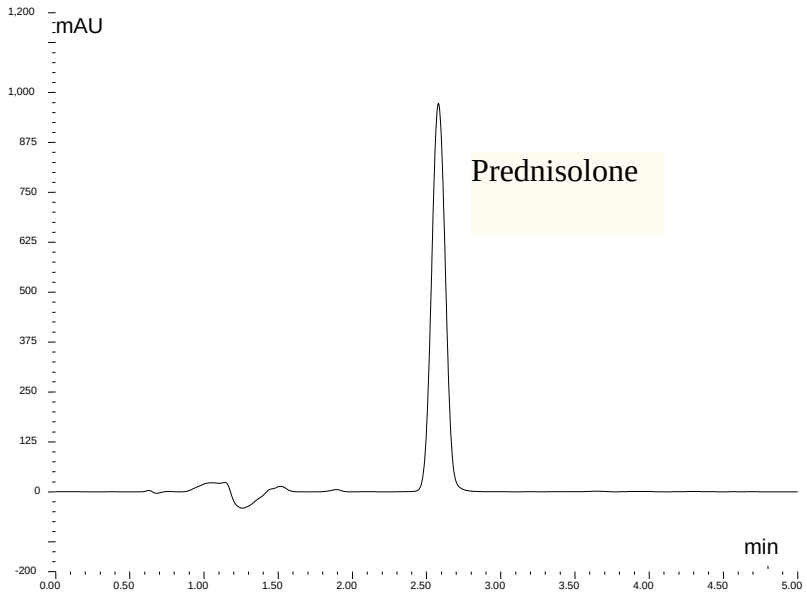

Figure 1: Chromatogram shows the HPLC separation of the commercially available standard of the active ingredient – presnisolone, which the tablets supplied will/will not contain.

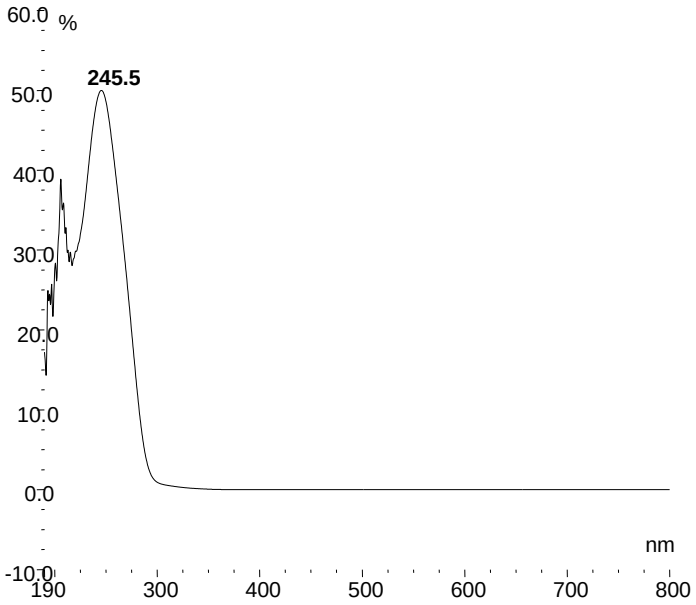

Figure 2: The Absorbance spectrum of prednisolone generated by Chromeleon (Dionex software) and the authenticity of the drug in the tablets was decided from this spectrum.

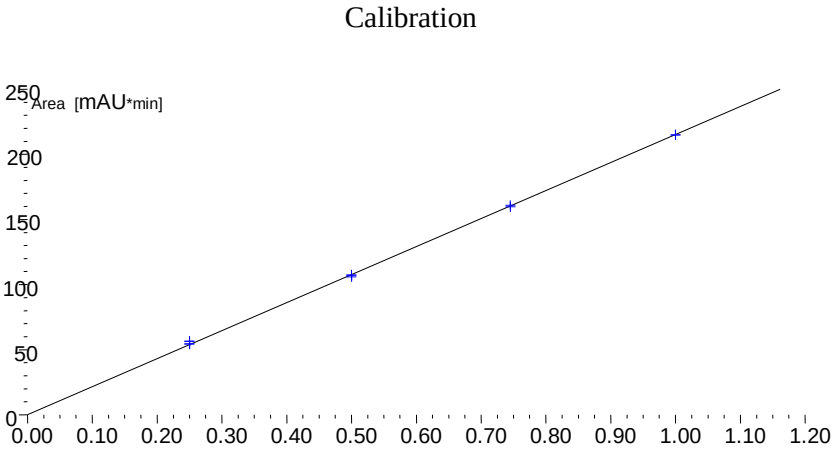

Figure 3: The calibration curve of prednisolone (0 - 1.0 mg/ml) generated by Chromeleon (Dionex software). The amount of active ingredient detected in the tablets was determined from this curve.

RESULTS:

The plot for tablets (4 in of each; authentic drug n=4, placebo n=4) reported to contain the active ingredient and the placebo is shown below. Amounts indicated were measured by HPLC and calculated against the calibration plot, figure 3.

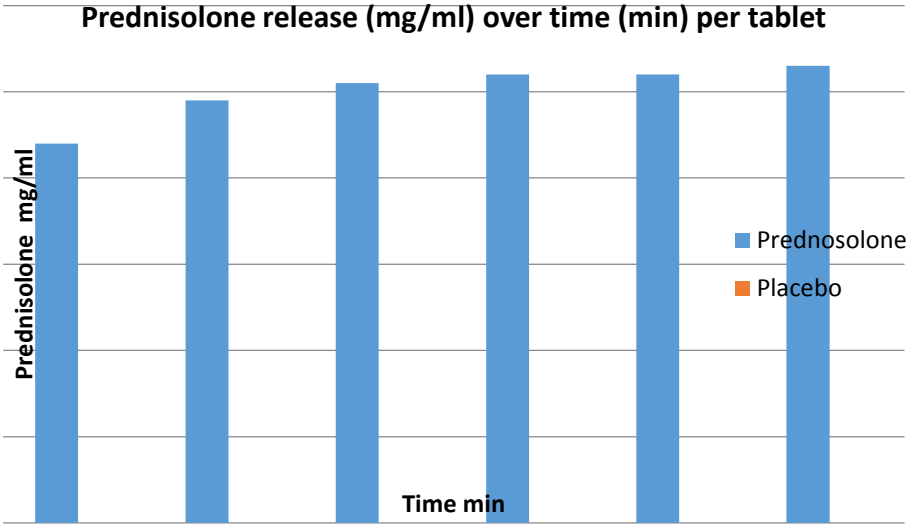

Table of data points that are drawn in Plot above:

Prednisolone (mg/ml) release with time - min

Time-mins	Active	Placebo
10	0.0044	0.0000
20	0.0049	0.0000
30	**0.0051**	**0.0000**
40	0.0052	0.0000
50	0.0052	0.0000
60	0.0053	0.0000

USP rules stipulate that at 30 min greater than 70% of the tablet should be detected in the dissolution media and the calculated values per tablet are as follows:

Tablet	mg/ml	
	100%	70%
Pred 5.00 mg	0.0056	0.0039

CONCLUSION:

The prednisolone tablets tested show the anticipated tolerance as stipulated by the USP rules giving the amount of active ingredient (greater than 0.0039 mg/ml) that should be released into solution over 30 mins in each case (actual amount released is 0.0051 mg/ml; see the plotted data above). These tablets exhibit the stipulated dissolution profile that should lead to therapeutic bioactivity. The expected peak for the active ingredient was not present on the chromatogram of the solution of the tablets labelled placebo.

APPENDIX 20: PATIENT PHOTO CONSENT FORM

RED MEDICAL CLINIC

PHOTOGRAHY CONSENT FORM

I hereby confirm that I give consent for the photographs to be taken of me. I understand the material has educational value. I consent to the material being shown to appropriate professional staff and used in educational publications, journals, textbooks and used in any other form or medium including all forms of electronic publication or distribution anywhere in the world. As a result, I understand that the material may be seen by the general public. All or part of the material may be used in conjunction with other photographs, drawings, videotape images, sound recordings or other forms of illustration. Efforts will be made to conceal my identity but full confidentiality is not guaranteed.

Name: Signature: Date:

Consent obtained and witnessed by:

Name: Signature: Date: